

中華民國比較病理學會第十次比較病理學研
討會
(泌尿系統專題)

主辦單位：中華民國比較病理學會
三軍總醫院

時間：中華民國八十六年十一月二日
地點：三軍總醫院研究大樓視聽教室

中華民國比較病理學會第十次比較病理學研討會

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議程表

時間：中華民國八十六年十一月二日（星期日）上午 08:00~下午 15:30

地點：三軍總醫院研究大樓視聽教室（台北市汀州路三段 8 號）電話：(02)3651003

主辦單位：中華民國比較病理學會

三軍總醫院

時 間	議 程
08:00- 08:45	報到
08:45- 09:00	開幕致詞
	Section 【1】
09:00- 09:15	Case 76 Si-kwang Liu (劉錫光 博士), DVM, PhD
09:15- 09:30	Case 77 J-P Juch (祝志平 醫師), MD, MS
09:30- 09:45	Case 78 Mu-Tsung Tsai (蔡睦宗 獸醫師), DVM, MS
09:45- 10:00	Case 79 Mei-Ling Chen (陳美玲 醫師), MD
10:00- 10:30	Coffee Break
	Section 【2】
10:30- 10:45	Case 80 Chung-Tiang Liang (梁鍾鼎 獸醫師), DVM, MS
10:45- 11:00	Case 81 Chu-The Chen (陳朱德 醫師), MD
11:00- 11:15	Case 82 Hsiang-Sen R. Yeh (葉祥森 醫師), MD, MS
11:15- 11:30	Case 83 Hans Chen (陳憲全 獸醫師), DVM
	Section 【3】
11:30- 11:45	Case 84 T-Y. Lin (林智一 醫師), MD
11:45- 12:00	Case 85 Chen-Hsuan Liu (劉振軒 博士), DVM, PhD
12:00-13:30	Luncheon (中華民國比較病理學會理監事聯席會議)
13:30- 13:45	Case 86 Ming-Dar Tzou (鄒明達 醫師), MD
13:45- 14:00	Case 87 Hui-Chuan Cheng (程慧娟 醫師), MD
	Section 【4】
14:00- 14:15	Case 88 Fur-Jiang Leu (呂福江 醫師), MD, PhD
14:15- 14:30	Case 89 Cheng-Chung Lin (林正忠 獸醫師), DVM, MS
14:30- 14:45	Case 90 Teh-Hsiou Huang (黃德修 醫師), MD
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15:00- 15:30	討論

Comparative Pathology Case 76

Contributor: Si-kwang Liu (劉錫光), DVM, PhD

The Animal Medical Center, New York, New York 10021, USA; Pig Research Institute, Taiwan, ROC

Clinical History: Chronic active lymphoplasmacytic conjunctivitis was diagnosed by biopsy in a 5-year-old, male, Scot Fold cat with mucoid ocular discharge on April 8, 1993. The cat had been examined in November 1995 at the Animal Medical Center because of a distended abdomen. Ultrasound examination of the abdomen revealed large kidneys containing numerous, variably-sized cysts; the left kidney was larger than the right. Bilateral polycystic kidney was diagnosed in December 1995. When the cat was examined in March 1996, it had lost weight and the kidneys were further enlarged, the PCV was 35%. The cat in July, was mildly azotemic with increasing polyuria and polydipsia, low urine specific gravity, and sinustachycardia. The heart rate of 204, a grade I-II/V, systolic murmur was detected by cardiac examination. On the last clinical visit May 28, 1997, the cat had been depressed, anorexic, lethargic, and cachectic for 2 weeks. Severe azotemia, isosthenemia, and renal failure were documented in observed. Results of blood chemistry profile, urinalysis and hemotologic profile are summarized in Table 1, 2 and 3. The owner elected to euthanatize the cat.

Table 1 Blood Chemistry Profile

	12/6/95	3/3/96	6/30/96	5/28/97
Total Protein	7.5	8.1	7.0	7.8
Globulin	4.1	3.2	3.0	4.7
BUN	36.5	32.1	40.1	172.9
Na	156.0	155.0	155.0	143.7
K	5.1	4.7	4.7	1.9
Cl	11.9	12.1	12.4	10.6
Glucose	87.0	67.0	77.0	177.0
CPK	135.0	116.0	247.0	123.0
Creatine	2.1	2.0	2.3	9.7
Ca	9.4	9.1	8.6	4.5

Table 2 Urinalysis

	12/16/95	3/2/96	6/31/96	7/14/96	5/28/97
S. G.	1.024	1.021	1.017	1.016	1.011
pH	6	6	7.5	6	6
Protein	trace	trace	1+	trace	1+
Glucose	--	--	100	100	100
Blood	--	--	1+	2+	4+

Table 3 Hemotologic Testing

	6/30/96	5/28/97
RBC	16.3	9.1
WBC	7.8	4.7
HCT	36.1	22.6
MCV	45.2	48.3
MCH	13.6	14.9
MCHC	30.2	30.8
HGB	10.9	6.9

Diagnosis: Polycystic kidney bilateral and renal failure

Gross Findings: The cat was thin, weighed 2.925 kg, and measured 45 cm length. Both of the kidneys were cystic. The right kidney measured 8.2×6.3×4.1 cm, and contained numerous cysts filled with clear fluid. The left kidney, 7.5×6.1×4.7 cm, had most of the renal parenchyma replaced by fluid-filled cysts. The right ventral margin of the tongue had an area of yellowish-white, ulcerative surface that measured 1.6×0.2 to 0.4 cm. The heart weighed 18.3 gms. Several membraneous moderator bands (false tendons) were connected between the ventricular septum and left ventricular free wall. Thickness of the ventricular septum and left ventricular free wall were 6 mm, and the right ventricular free wall was 2 mm.

Histopathological Findings: The renal parenchyma was destroyed by numerous large cysts lined by cuboid or flat, columnar epithelial cells. Cells were enclosed by a thin capsule. Atrophic glomeruli, tubules filed with inspissated urine, and excessive interstitial fibrous connective tissue were seen in the adjacent parenchyma. Urinic glossitis was observed in the tongue. Hypertrophic cardiocytes and arteriosclerosis were observed in the left ventricle.

Discussion: Polycystic kidneys are not common in animals. They are observed in calves, horses, pigs, dogs, and cats. In human beings, polycystic renal disease is found in 1 of 500 autopsies and 1 of 3,000 hospital admissions and accounts for approximately 10% of endstage renal failure.

Polycystic renal disease in cats is most likely a congenital disorder. The signs usually appear at the age of 3 to 4 years and progress to renal failure at the age of 5 to 7 years. Polycystic disease in cats is similar to the disease in human patients, in whom symptoms usually appear in the third or fourth decade and progress to chronic renal failure. Human polycystic disease is hereditary, autosomal, and dominant, and is linked in most families to the alpha hemoglobin gene complex and the phosphoglycerate kinase genes on the short arm of chromosome 16.

It has been recently reported that mice overexpressing hepatocyte growth factor/scatter factor in the kidney and serum demonstrated prominent tubular cystic disease and progressive to premature death from renal failure in transgenic mice.

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Comparative Pathology Case 77

Contributor: J-P Juch (祝志平), MD, MS

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Clinical History: A 65-year-old man, suffered from right flank pain and fever for 3 days. The past history revealed urinary bladder stone (1979) and right ureteral stone (1984). The KUB showed multiple right renal stones (2.4×2 cm) and right upper ureteral stone (4×2 cm). The renal sonography showed hydronephrosis, renal stones & ureteral stone. Laboratory examinations showed elevated uric acid (9.2 mg/dl), but no anemia (Hb: 12.8), no leukocytosis (WBC: 9250/ul). Urinalysis showed pyruia (numerous WBC/HPF and 9~11 RBC/HPF). Subcapsular nephrectomy was performed and OP findings showed severe adhesion and intense pyelonephritis. Ureteral stricture, just below the ureteral stone, was noted.

Diagnosis: 1. Xanthogranulomatous inflammation with nephrolithiasis, kidney, right.
2. Ureteral stone, right.

Gross Findings: The kidney submitted from subcapsular nephrectomy, measured 8.3×3.6×3.6 cm & weighed 50 gm. The surface was hemorrhagic and, irregular. The cut surface showed diffuse yellowish granuloma-like nodules (up to 1.0 cm in diameter) replacing part of the renal tissue. There were also calcified areas in the renal pelvis. A ureteral stone, 4 cm in length is noted with a distal stricture (2 mm in diameter).

Histopathological Findings: The yellowish granuloma-like areas discribed above revealed to be xanthogranulomatous inflammation of kidney with collections of xanthomatous foamy cells, focal PMN infiltration & calcification. Atrophy & thyroidalization of renal parenchyma were marked.

Histochemistry Results: 1. PAS stain showed granules but no bacterial fragment was found.
2. Acid fast stain showed no evidence of tuberculosis.

Discussion: Xanthogranulomatous pyelonephritis (XGP) is an unusual, special form of infection-associated chronic interstitial nephritis that may be related to poor urinary drainage or parenchymal hemorrhage in patient with *E. coli* or *Proteus* species infections. This inflammatory process results in focal or diffuse renal enlargement and nonexcretion. The infection begins in renal pelvis to medulla, cortex, the extra-renal extension of the inflammatory process is common, and may involve the peri-nephritic space, para-renal space, psoas muscle, flank muscle, diaphragm and skin. XGP grossly displays soft yellow nodules

(may be confused with renal cell carcinoma) and cavities within the thinned parenchyma, particularly around the calyceal system and often with stone formation. The tumor-like inflammatory lesions of the kidney (XGP, malakoplakia) are of importance of the pathologist because they may be confused clinically, grossly and histologically with renal cell carcinoma. XGP may be a variant of malakoplakia or vice versa but differs from it by the absence of Michaelis-Gutmann bodies (lamellar calcified bodies containing iron and calcium).

In the past, XGP often had been misdiagnosed as renal cell carcinoma. Newer investigative modalities and increased awareness of XGP should make preoperative diagnosis possible. (The typical appearance at CT scan of central lithiasis and multiple rounded areas of low density with enhancing rim [bear paw sign]). Although the radiologic picture may be helpful, correlation with the clinical findings is still required (as with all renal lesions). The symptoms includes a palpable flank mass (52%), flank pain or flank tenderness (55%) and most patients had history of renal stone, obstructive uropathy, DM or urologic surgery. Laboratory data often reveals anemia (67%), leukocytosis (40%), pyuria and renal insufficiency. Urine culture often reveals *E. coli* or *Proteus mirabilis*.

Microscopically, there are sheets of foamy macrophages diffusely and in clusters, often with cholesterol crystals and granulomas. Plasma cells and lymphocytes are found with neutrophils when active infection is still present. Giant cells are occasionally noted. Tissue destruction can be widespread, with necrosis of all renal elements and granulation tissue formation.

Differential Diagnosis: 1. Malakoplakia.
2. Renal cell carcinoma.

Treatment: 1. Antibiotics for active infection.
2. Correction of obstruction if still present.
3. Nephrectomy, but may be difficult owing to intense pyelonephritis.

Diagnostic Criteria:

1. The presence of large quantities of foamy lipid within histiocytes, which comprise the predominant infiltrative cells.
2. Most of the macrophages are large or very large foam cells with pale granular cytoplasm which contains lipid made up to neutral fat and cholesterol ester. (PAS-positive granules could be demonstrated in the cytoplasm).
3. Ultrastructurally, the PAS-positive granules are cytosomes, containing myelin figures & sometimes, bacterial fragments.
4. Absence of Von Kossa-positive Michaelis-Gutmann bodies (D/D malakoplakia).
5. Other inflammatory cells (plasma cells, lymphocytes or neutrophils) and large foci of necrosis may also be present.

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Comparative Pathology Case 78

Contributors: Mu-Tsung Tsai (蔡睦宗), DVM, MS; Hsing-Hsung Hung (洪信雄), DVM, MS
Livestock Diseases Diagnostic Laboratories of Pingtung Prefecture

Clinical History: A poultry farm reared about 3600 native chickens in Pingtung prefecture. The accumulative morbidity and mortality within two weeks period were about 13.8% and 20%, respectively. Clinically, The affected flock showed signs of unthriftiness, anorexia, weakness of legs, weight loss, and pale head parts. The owner sent six affected and dead native chickens, 70-day-old, to our laboratories for pathological diagnosis.

Diagnosis: Marek's disease in native chicken

Gross Findings: The predominant lesions were lymphomas of various visceral organs, including heart, liver, spleen, lung, kidney, mesentery, proventriculus, skin of cervical and head parts. Nodular tumor-like growths, single or multiple ones ranging from 0.1~1.5 cm in diameter, were found within and extending from the parenchyma of the organ. These were firm and smooth when cut and whitish gray or yellow-orange in color. The bursa of Fabricius became atrophic.

Histopathological Findings: There were three types of lesions in visceral organs. The main Type A lesion consisted of diffusely proliferating lymphoid cells, which include primitive activated reticular cells, lymphoblast, Marek's disease cells and small, medium and large lymphocytes. The type B lesion was characterized by diffuse, light to moderate infiltration by small lymphocytes, plasma cells and an occasional lymphoblasts. The type C lesion consisted of small areas of lightly scattered lymphocytes and plasma cells. Interfollicular lymphoid infiltration, hypoplasia, and cyst formation were also seen in the bursa of Fabricius.

Discussion: Marek's disease is a lymphomatous disease of the domestic chicken in which lymphoproliferative infiltration and demyelination of peripheral nerve are common features. It was first described by the Hungarian veterinarian Jozsef Marek in 1907. Neural involvement, leading to paralysis, was the most evident manifestation and the names of fowl paralysis, range paralysis and neurolymphomatosis were commonly applied. During the late 1950s and through the 1960s a more virulent form of Marek's disease (MD) was described, characterized by up to 40% mortality in layers and lesion frequency in broilers of up to 10% in selected flocks. Although nerve lesions continued to be present, The predominant lesions were pleomorphic lymphomas of various visceral organs, including heart, liver, spleen, gonad, lung, muscle, proventriculus, kidney, and others. Nerve lesions were also common. This disease syndrome was designated as "acute leukosis" or "visceral lymphomatosis" to differentiate it

from the earlier, "classical MD." Such virus strains were later included in the virulent (vMDV) pathotype in non-vaccinated and HVT-vaccinated chickens. During the late 1970s, a still more virulent form of MD was described, characterized principally by higher than expected frequency in flocks vaccinated with HVT and designated as members of the very virulent (vvMDV) pathotype. In 1995, Viruses isolated, between 1987~1995, were designated vv+MDV. Ocular lesions and corneal opacity were induced at high rates by nearly all viruses of vvMDV and vv+MDV pathotypes but not by vMDV isolates. The factors that favor the evolution of MDVs toward greater virulence are not known. However, it seems likely that this process might occur more rapidly in chicken populations with high levels of vaccinal immunity or genetic resistance. Indeed, the two previous waves of virulence increase each commenced about 6 yr following the introduction of HVT and bivalent vaccines. In the present case, Visceral form of Marek's disease is the first priority of diagnosis. The pathotype of the virus strain yet need to be done.

Lymphoid leukosis (LL) is the principal disease to be considered in differential diagnosis of MD. However, LL may be differentiated from MD by the common involvement of the bursa of Fabricius, uniform blast morphology, pyroninophilia, and presence of B-cell markers and absence of MATSA on tumor cell. Other diseases that may present confusing gross lesions or paralytic signs are Reticuloendotheliosis (RE), myeloblastosis, erythroblastosis, carcinoma of the ovary, other neoplasms, riboflavin deficiency, tuberculosis, histomoniasis, genetic gray eye, Newcastle disease, avian encephalomyelitis, perosis, and joint infections or injuries.

MDV was classified as a gamma-herpesvirus on the basis of its biological characterization. However, the overall genome structure of MDV is more similar to those of human alpha-herpesviruses (e.g., varicella-zoster virus and herpes simplex virus). Integration of retroviral provirus into a herpesviral genome could result in a mutated herpesvirus with increased virulence. Three predominant types of gross pathological lesions due to HVs can be differentiated. These include: lytic-inflammatory followed by neoplastic response in Marek's disease (MD) of chickens; haemorrhagic-diphtheric response in all cases of DVE and ILT and in Psittacines, haemorrhages in either the trachea or gut; diphtheric-necrotic responses in pigeon, owls, falcons, birds of prey, black storks and white storks, cranes and bobwhite quail the diphtheric lesions being located usually in the pharynx and upper part of the oesophagus but sometimes in the colon and cloaca, while multifocal necrotic lesions are grossly visible in liver, spleen, bone marrow and sometimes kidney. MDV has been subdivided into three serotypes: serotype 1 (MDV1), oncogenic strains (Md+) of MDV and attenuated or nononcogenic variants (Md-) derived from them; serotype 2 (MDV2), naturally occurring apathogenic strains; and serotype 3 (MDV3), herpesvirus of turkeys (HVT). Commercially available vaccines have been derived from all three serotypes, for use either alone or in combination. The Marek's disease vaccine was the first practical effective cancer vaccine in any species and should be recognized as a major advance in medical science. The findings

that MDV infection may lead to arteriosclerosis in chickens have profound implications as a model for the same condition in humans.

MDV spreads rapidly from infected to uninfected birds. The virus is present in desquamated feather follicle epithelial cells and in oral, nasal, and tracheal secretions. The feather follicle cells are the most important source of infection and are responsible for the infectivity of dander, poultry house dust and litter. Airborne spread of virus and infection via the respiratory tract is considered to be the most important route. There are a number of factors which affect the appearance and severity of Marek's disease in an individual chicken and the severity of an outbreak of disease in a flock. These factors include the genetic constitution of the chicken, sex, age, the strain of virus, and stress. The hosts include chicken, guinea fowl, turkey, jungle fowl, pheasants and others.

Diagnostic Criteria:

1. Characteristics of Marek's disease lesions of importance in differential diagnosis include nerve or visceral involvement, absence of bursal lesions, and pleomorphic lymphocytes comprising lesions, some of which exhibit MATSA and only few of which are positive for IgM.
2. A diagnosis can usually be made after consideration of the history, the age of the birds affected, and the location of the neoplastic lesions in a generous sample of typically affected chickens. Few epornitic diseases resemble Marek's disease except for lymphoid leukosis and reticuloendotheliosis.
3. Marek's disease often occurs in 2-5 month old chickens but can also occur after the onset of egg production.
4. DNA amplification by polymerase chain reaction (PCR), and restriction enzyme analysis have offered new approaches to comparative analysis of viral DNA.

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Comparative Pathology Case 79

Contributors: Mei-Ling Chen (陳美玲), MD; Kun-Tu Yeh (葉坤土), MD; Huei-Mei Chang (張惠媚), MD; Shiau-Fang Yang (楊曉芳), MD

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Clinical History: The 49-year-old female was a victim of DM with poor control. She sought medical attention due to dizziness and general weakness for 2 days. In ER, laboratory study showed blood sugar: 923 mg/dl, BUN: 59.9 mg/dl, Creatinine: 3.1 mg/dl, WBC: 18300/ul (segment: 91%), urine RBC: numerous, urine WBC: 20~30, urine ketone (+). Renal ultrasonography revealed left renal staghorn stone with possibility of right retroperitoneal or perirenal abscess. Right nephrectomy was later performed.

Diagnosis: Emphysematous pyelonephritis

Gross Findings: The resected specimen consists of right kidney measures 13.2×7.5×5.5 cm in size, a segment of ureter measuring 6 cm in length and 0.5 cm in diameter and perirenal fat tissue fragments measuring up to 3.7×2.5×1.2 cm in size. The kidney is enlarged and hemorrhagic. The cut surface shows subcapsular grayish patch and randomly distributed cystic spaces. Papillary necrosis is also noted.

Histopathological Findings: It shows large empty spaces, effectively gas pockets in both cortex and medulla with severe inflammation extending through the capsule into the surrounding perirenal tissue. Widespread abscess and infarct with thrombosis are present. Focal segmental sclerosis and global sclerosis are seen. The ureter reveals leukocytic infiltrate in the wall.

Discussion: Emphysematous pyelonephritis is a rare, life-threatening form of bacterial infection producing accumulation of gas in the renal and perirenal tissues. It occurs principally in diabetics, often with associated obstruction.

The responsible agents have in common the ability to ferment lactose and glucose with the production of carbon dioxide. Most cases have been due to gram-negative rods, predominantly *E.coli* (68 percent), with *Klebsiella* (9 percent), *Aerobacter* and *Proteus* seen as well. Fourteen percent of the patients have had mixed infection. At least two cases of *candida* species have been reported. Importantly, no cases related to *Clostridium* have been described.

Emphysematous pyelonephritis is typically a severe process with widespread abscess and necrosis, including papillary necrosis. Not infrequently there is vascular involvement, with arteritis, thrombosis, and resulting infarcts. Often the process extends straight through the

renal capsule into the surrounding perirenal tissue. The characteristic feature is the presence of large, empty spaces, effectively gas pockets, confined to the areas of severe inflammation. Computed tomography identifies accurately the presence of gas and its extent.

Ultrasonography also is rapid and noninvasive; it gives appearance that, although not diagnostic, are highly suggestive of gas. The 90 percent survival has been obtained with a combination of medical and surgical management. Nephrectomy may be indicated, depending on the degree of recoverable function in the affected kidney, the status of opposite kidney, and the general condition of the patient.

Diagnostic Criteria:

1. Randomly distributed gas bubbles in both cortex and medulla.
2. Severe acute and chronic necrotizing pyelonephritis with abscess.
3. Papillary necrosis.

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Comparative Pathology Case 80

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Clinical History: A 14-month-old, male specific-pathogen free (SPF) inbred spontaneously hypertensive rat (SHR/N(BR)) was from the colony originally introduced from National Institute of Health (Washington, DC. U.S.A.). The rat developed no clinical signs. Because of routine health monitoring, the rat was euthanized by CO₂ asphyxiation. HR 401.0±6.9, SBP 157.7±7.0 (mmHg), DBP 127.0±2.0 (mmHg), MBP 137.0±1.0 (mmHg).

Diagnosis:

1. Glomerular sclerosis and hyalinosis, segmental, focal, chronic, moderate, SHR rat
2. Benign hypertension, SHR rat.

Synonyms: Old rat nephropathy, chronic progressive nephrosis, glomerulosclerosis, progressive glomerulonephrosis.

Gross Findings: This rat was obese. Both kidney have tan appearance and granular surface marked by pitting. Other organs are grossly normal.

Histopathological Findings: Different stages of glomerulosclerotic lesions are present in this case. The key characteristics are eosinophilic amorphous proteinaceous casts in dilated renal tubules and thickened Bowman's capsules. In addition, 20 to 30% of the glomeruli, most of the juxtamedullary population, undergo partial or total sclerotic changes with increased of mesangial matrix and atrophy of capillary loops. Quite a few intercapillary and mesangial cells are pyknotic and swelling of the nuclei, some assuming bizarre shapes and staining intensely with hematoxylin. Disturbed segments of the glomerular tufts become attached to the thickened Bowman's capsules and the nearby epithelium undergoes atrophy as well as regeneration. More advanced sclerotic glomeruli show homogenous hyalinized eosinophilic materials accumulation, particularly at the periphery or even whole of glomerular tufts. The interstitium around diseased nephrons is seen to be infiltrated by mononuclear cells and lymphocytes and is fibrotic with giant cells formation in focal areas. The lesions are arranged in a radiating manner and involve the outer as well as the inner cortex. Apart from mild medial hypertrophy, interlobular and arcuate arteries do not exhibit pathological lesions.

Other organs, including lung, testis, jejunum, duodenum, pancreas, heart, liver, and spleen show no significant lesions.

Discussion: In human, 90 to 95% of hypertension is idiopathic and apparently primary (essential hypertension). Of the remaining 5 to 10%, most are secondary to renal disease or, less often, to renal artery stenosis, endocrine, vascular or psychogenic factor. Both essential and secondary hypertension may be either benign (stable over years to decades, compatible with long life), or malignant (rapidly rising blood pressures, if untreated, leads to death within a year or two).

The spontaneously hypertensive (SHR) rat serves as a comparative model that has many characteristics resembling those found in essential hypertension of human. The SHR rat was developed by Dr. Kozo Okamoto and Dr. Aoki in 1959. They examined the blood pressures of several hundred rats from Wistar colony of the animal center at Kyoto University, Japan (WKY strain). One of the male rat examined exhibited blood pressures of 145~175 mmHg. A female rat with blood pressures of 130~140 mmHg was chosen for mating with this male. Successive brother sister matings were continued in order to produce the inbred strain of SHR rats, which was obtained in October, 1969 (twentieth generation). In the most of SHR rats, hypertension (over 150 mmHg) develops by the fifth week, and is maintained in adult animals at a higher level (frequently over 200 mmHg). The average blood pressure mean \pm SD in males and females F30~32 Generation is 184 \pm 17, and 178 \pm 14, respectively, at the age of 10 weeks. The similarities between essential hypertension in man and spontaneously hypertension in rats include the following:

1. Polygenic inheritance.
2. No specific pathogenic mechanism.
3. Similar course, the blood pressure rise with age.
4. Cardiovascular complications include left ventricular hypertrophy and dilatation, often leading to congestive heart failure, hemorrhagic stroke, nephrosclerosis, malignant hypertension with fibrinoid necrosis of arterioles, atherosclerosis of the coronary and cerebral arteries.
5. Similar hemodynamic changes.
6. Related to high sodium intake.
7. Response to antihypertensive drugs.

There are three hypotheses for pathogenesis of essential hypertension, including genetic defect in renal sodium excretion, or in sodium/calcium transport, or causing neurohormonal release.

In malignant form of SHR rat, the affected rats even young still had subcutaneous and facial edema, dyspnea, cyanosis, and malaise and survived from 5 to 14 days after the onset of clinical signs. At necropsy, lesions include hydrothorax, ascites, cardiomegaly, thickened ventricular walls, left atrial dilatation, thrombosis and hepatomegaly. Microscopic findings were myocardial and cerebral infarction, interstitial fibrosis, atherosclerosis and angioneclerosis.

These lesions were similar to our findings in other SHR rats when at necropsy in our center but to a lesser extent in this case.

Hypertensive nephropathy in SHR rat resembles the nephropathy seen in some cases of human essential hypertension. Hypertension is generally supposed to enhance the development and degree of glomerulosclerosis and proteinuria in SHR rat. However, several studies show elevated protein excretion in SHR rat is not a secondary consequences of systemic hypertension, and triple drug regimen (a combination of hydralazine, reserpine, and hydrochlorothiazide) and enalapril treatment in SHR rat delayed but could not prevent the eventual development of albuminuria, nephropathy and vessel wall hypertrophy. It remains a question whether a nephropathy is necessary and sufficient for the development and maintenance of hypertension or is simply a consequence of this disease.

Hypertensive nephropathy in SHR rat need to differentiate from chronic progressive nephrosis (CPN). The CPN is the most common spontaneous renal disease in aging rats. Lesions are rarely observed in rats less than 1 year old but by 2 years of age 75% or more may have lesions. Albino strain and stock have higher incidence. Sprague-Dawley, Fisher 344, Wistar, and Marshall rats are more susceptible than other strains. It occurs with lower incidence in Osborne-Mendel, Buffalo, Long-Evans, WAG/Rij and BN/Bi/Rij rats.

Male rats are more susceptible than females, castrated male are less susceptible. The key features of CPN are tubular dilatation with eosinophilic proteinaceous casts, and basement membrane thickening. Variable stages of interstitial inflammation and hyperplastic and/or hypertrophic tubular and glomerular changes are present. The CPN can develop in Milan normotensive strain (MNS) rather than Milan hypertensive rat (MHS) indicate that hypertension is not necessarily followed by these glomerular lesion. Similar report show proteinuria and mesangial IgM deposition apparently precede of a focal sclerotic glomerular lesion in aging rats. The causative factors in CPN remain quite obscure. Reduction in caloric and protein content of diets has correlated with a decrease in severity of the disease.

Diagnostic Criteria:

1. Most common in 1 to 2 year-old, male albino rats.
2. Renal tubular dilatation with eosinophilic proteinaceous casts.
3. Basement membrane thickening and collapse of capillary loop, and capillary lumen occluded by electron-dense, PAS (+) materials, epithelial podocytes fusion.
4. Glomerular sclerosis and hyalinosis.
5. Mesangial IgM deposition (?)

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Comparative Pathology Case 81

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Clinical History: A 49-year-old female presented with hematuria and left flank knocking pain 7 years ago and intravenous pyelogram revealed no evidence of stone. This time she was admitted due to fever and itching skin rashes for 3 days. During admission, urinalysis showed hematuria. Sonography of kidney showed a right renal tumor measuring 3.7×3.7 cm. CT scan and angiogram revealed a protruding renal tumor in the upper pole of the right kidney. Nephrectomy was performed. Post-operation condition is stable.

Diagnosis: Angiomyolipoma

Gross Findings: A well-demarcated oval tumor, measuring 4×3×2.5 cm, elevates the renal capsule, producing a bulging mass with bosselated surface. The cut surface is grayish brown and lobulated.

Histopathological Findings: Microscopically, the tumor is composed of a variable admixture and organization of mature adipose tissue, blood vessels, and smooth muscle. The adult-type fat cells are scanty, unevenly distributed and showing a large, central lipid vacuole and an eccentric pyknotic nucleus. Smooth muscles are distributed throughout the tumor, not only between the fat cells but also around vessels and in large solid sheets of whorled and interlacing fascicles. The vascular component consists of large thick-walled vessels resembling arteries with walls of varying thickness, eccentrically placed lumens, and subintimal fibrosis.

Discussion: The term angiomyolipoma was first used by Morgan and associated in 1951; however, this tumor was initially described in 1911 by Fischer, who also documented its frequent association with the triad of mental retardation, epilepsy, and adenoma sebaceum (tuberous sclerosis complex). Angiomyolipoma is a tumor composed of varying admixtures of blood vessels, smooth muscle cells, and adipose tissue. Patients with angiomyolipomas may present with acute flank pain, a palpable mass and hematuria.

The fatty tissue in the tumor is detected as a strongly hyperechoic lesion in the mass by ultrasonography and an extremely hypodense component by CT scan. Tumor with scant fat at CT and hyperechoic pattern at sonogram may be indistinguishable from renal cell carcinoma. Angiomyolipomas may arise in the cortex or medulla and are frequently polar. They are round-to-oval, bulging masses with a smooth or bosselated surface, and can be up to 20 cm in diameter, with a mean of 9.4 cm. Multiple satellite masses that are less than 1 cm in diameter may be present. The cut surface is yellow to gray, depending upon the proportion of fat and smooth muscle,

and is lobulated.

Angiomyolipomas are uncommon lesions with a prevalence of 0.3%~3%. They constitute only 1% of surgically confirmed renal tumors. They are seen in two distinct clinical settings: sporadic (isolated) or in association with tuberous sclerosis. The sporadic form are usually unilateral and solitary, typically seen in middle-aged patients (mean age, 43 years) with more common in women by at least a 4:1 ratio, and accounts for approximately 80%~90% of cases of angiomyolipoma.

While as many as 80% of patients with tuberous sclerosis may have angiomyolipomas, less than 40% of patients with angiomyolipomas have one or more features of the tuberous sclerosis complex, i.e., cutaneous lesions, retinal phacomias, and visceral or cerebral angiomas and cerebral neoplasms. However, if small (less than 1 cm) angiomyolipomas are included, the number of patients with tuberous sclerosis may even less.

In cases with an extreme predominance of fat, angiomyolipoma can be confused with lipoma. Tumors with scant fat may be confused with other mesenchymal tumors, such as leiomyoma or leiomyosarcoma. Extensive sampling may be necessary in above condition to identify three components of the tumor. Angiomyolipomas may also be found in extrarenal sites such as regional lymph nodes, retroperitoneum, liver, fallopian tubes, adrenal, spleen, spermatic cord, and uterus.

Diagnostic Criteria:

1. Varying amounts of blood vessels, smooth muscle, and fat.
2. All three tissue types must be seen to establish the diagnosis.

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Comparative Pathology Case 82

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Clinical History: Patient is a 67-year-old man who suffered from painless gross hematuria one day before he visited for help. No other symptoms/signs related to GU problems except for frequency were noted. Cystoscope was conducted with the findings of enlarged prostate and bulging of mucosa with vague smooth polypoid surface contour over prostatic urethra area. Bladder stone was also found. The tumor and prostate were resected and were sent for pathological examination which is presented in this conference.

Diagnosis: Inverted papilloma of prostatic urethra

Gross Findings: Irregular bulging of mucosa over prostatic urethra with smooth surface contour. Tumor measures up to 2 cm in greatest diameter and is relatively well defined.

Histopathological Findings: The tumor consists of subepithelial growth of ramifying branching and anastomosing cords of epithelial cells which resemble the urothelial cells. Palisading of basal cells of the tumor strands are marked and are outlined with intact basement membrane. Focal squamous metaplasia and cystic change are present. Atypia is slight and mitotic activity is low in tumor cells. The overlying urothelium shows attenuated change. Some tumor strands are connected with the basal layer of the urothelium. The underlying prostate tissue shows nodular proliferation.

Discussion: Inverted papilloma is a rare tumor in urinary tract, comprising from less than 1% to up to 2.2% of transitional cell tumors reported by different groups. It was first described in detail in 1927 by Paschkis, a Viennese urologist, as an “adenoma-like polyp” of the urinary bladder. Inverted papilloma was coined by Potts and Hirst in 1963, and since then hundreds of cases has been reported in literature. The male: female ration is about 3:1 and the peak incidence is in 6th and 7th decades. The tumor mostly occurs in trigone area and urethral neck and other portions of urinary tract in less frequency, including lateral wall of bladder, pelvis and prostatic urethra. The most common presenting symptoms are hematuria and obstruction as the tumor most commonly occurs in the trigone and neck of urinary bladder.

The histologic characteristics of inverted papilloma have been categorized into two general types. Kunze et al in 1983 proposed this categorization---inverted papilloma of trabecular type and inverted papilloma of glandular type. Both types exhibit a characteristic endophytic growth pattern and are covered with a slightly hyperplastic or attenuated but otherwise unremarkable urothelium. The trabecular type consists of irregularly ramifying, intimately

anastomosing cords or strands of neoplastic urothelial cells which arise directly from the overlying transitional epithelium. The trabeculae have peripheral palisading of the cells in places. In addition, urothelial buds with downward proliferation are frequently encountered along the base of overlying urothelium, protruding into the loose stroma beneath and possibly resulting in the formation of new tumor strands. Similar bud-like structures are also seen originating of tumor trabeculae themselves forming secondary to tertiary invaginations. Other associated features are occasional squamous metaplasia and cystic change of different size in some of the solid strands. These cystic spaces are lined with flattened urothelial cells and filled with some homogeneous eosinophilic, weakly PAS-positive material. The tumor cells are uniform and resemble the basal cells of the normal transitional epithelium. Mitotic activity is scant. The glandular type is characterized by multiple round to oval solid nests of proliferated urothelial cells with pseudoglandular to true glandular structures lying closely within a loose stroma. The true glandular structures are lined with an inner layer of mucus secreting columnar epithelium surrounded by several layers of urothelial cells. Sometimes glandular metaplasia of an intestinal type with formation of goblet cells is seen.

The histogenesis of inverted papilloma was proposed to be different for these types of inverted papillomas by Kunze group. The trabecular type develops by proliferation of the basal cells of the transitional cell epithelium. The theory is supported by the presence of multiple bud-like basal proliferations of the urothelium overlying the tumor and the close resemblance of the trabecular cells to the normal basal cells. As for the glandular type, it might derive from cystitis cystica and glandularis. Three-step process was proposed. The first step is the formation of von Brunn's nests, which may become increasingly cystic and progress into cystitis cystica. The second step is the transition of von Brunn's nests or cystitis cystica into cystitis glandularis. The final step leads to a neoplastic transformation of cystitis cystica and glandularis, resulting in the formation of inverted glandular papilloma.

The neoplastic nature has been supported by in vivo experiment on rat that inverted papillomas were induced with N-butyl-N-(4-hydroxybutyl)-nitrosamine (a potent bladder carcinogen). However, inverted papilloma is generally solitary with rare multiplicity, very low recurrence rate and absence of progression which indicate a benign nature. Occasional coexistence with transitional cell carcinoma has been reported, but real transition from papilloma to carcinoma has yet to be proved. The rare cases of inverted papilloma with malignant transformation could be actually a well differentiated transitional cell carcinoma with marked inverted growth. Therefore, differential diagnosis should be careful. Inverted papillomas with high proliferative activity, manifested with high Ki-67 expression, and high immunoreactivity for p53 may be susceptible to malignant transformation.

The malignant potential of inverted papillomas is still controversial. More detailed studies and experiences including prolonged follow-up are needed for assessment of the biological behavior of these tumors.

Diagnostic Criteria:

1. Inverted configuration of growth pattern
2. Covered with non-tumor urothelium
3. Uniformity of the epithelial cells with no or slight atypia
4. Absence or rarity of mitoses

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Comparative Pathology Case 83

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Clinical History: The rats were intraperitoneally (i.p.) injected with test compound at different dose levels. The affected rats (higher dose) were quiet and inactive approximately 1-2 hours after injection and died another 6~8 hours later. No obvious clinical sign was observed in rats given lower dose of the compound.

Experimental Study: Group of 6 young adult female SD rats each were administered 1 dose a water-soluble fullerene derivative via i.p. injection at dose levels of 0, 500, 750, and 1000 mg/kg of body weight, or 12-repeated doses at 0, 0.6, 6.0, and 60 mg/kg. Following the administration animals in 1 dose treatment were observed for 2 weeks prior to euthanasia for pathologic evaluation, while animals in 12-repeated treatment were sacrificed 1 day following the last dose.

Compound-related effects were noted in rats at an administration dose of 500 mg/kg body weight or above in that most rats in the two higher dose groups were quiet and inactive following injection. Eleven rats died within 30 h after the injection. The remaining 5 rats were in the 500 mg/kg group and survived during the 2 weeks post-dose recovery period. Therefore, the LD50 was defined as approximately 600 mg/kg. The direct cause of acute death was believed to be nonspecific system-related toxic effects which were not determined. Grossly, the kidneys were paler and were considered to be target organ.

In the 12-repeated dose study, no rats died during the study. A significant decrease in final body weight, thymus, and heart weight but an increase in spleen weight were observed in these sacrificed rats that included 5 rats given one dose 500 mg/kg and 24 rats given 12 repeated dose at different dose levels. Also a statistically and biologically significant increase in aspartate aminotransferase, but decrease in triacylglycerol were noted in the serum biochemical analysis. No BUN or creatinine alteration was noted.

Diagnosis: Phagolysosome-overload nephropathy

Histopathological Findings: The slide contains 3 sections of kidneys from 3 rats that include one acute death rat (kidney A) given the compound at a dose of 1000 mg/kg of body weight, one sacrificed rat given a dose of 500 mg/kg (kidney B), and another sacrificed rat given 12 repeated dose of 60 mg/kg (kidney C). The histologic features of the kidney A were a diffuse

massive necrosis and lysis of tubular epithelium involving primarily the outer cortex labyrinth of kidney. Kidney B and C showed vacuolar degeneration of the tubular epithelium of the labyrinth portion outer cortex primarily involving proximal and distal convoluted tubules. These degenerated tubular epithelium had numerous cytoplasmic vacuoles containing granular cores. No PAS positive material was demonstrated for these vacuoles or granular cores under the special stain. These vacuolar changes with inclusions in the epithelium were believed similar to the phagolysosome-loaded renal tubular epithelium, described as phagolysosome-overload nephrosis (1).

Ultrastructural Findings: The ultrastructural features of the compound-induced nephropathy correlated with the light-microscopic findings of numerous cytoplasmic vesicles and inclusions, primarily within the proximal convoluted tubules. Ultrastructurally, the cytoplasmic inclusions were characterized by phagolysosomal complexes of varying in size, each consisting of numerous smaller laminated or encircled electron-dense (E-D) band bodies. Many complexes also contained larger, fused membranous E-D bodies were similar to residual bodies. Some formed large laminated whorl-like bodies.

Discussions: The phagolysosome-overload nephrosis or phagolysosomal nephropathy is defined as the presence of numerous phagolysosomes in the tubular epithelium of kidney (1). The mechanism of renal injury in the present study is not well defined, but the kidney is considered to be the primary target organ that eliminated the compound (2). The compound induces a distinct phagolysosomal nephropathy that may serve as a biological marker in toxicity screening test for a series of synthesized water-soluble fullerenes (3). The compound induced renal effects in rats develops only after injection. No compound effect was induced in rats when the compound was administered orally (4).

The phagolysosomal nephropathy was characterized by the presence of vacuolar degeneration in the tubular epithelium of the renal outer cortex primarily affecting the proximal and distal convoluted tubules (4,5). The renal effects detected under light microscope were confirmed electron microscopically as the presence of numerous varying in size, phagolysosomal and lysosomal inclusions within the vesicles or vacuoles of the cytoplasm. These loaded inclusions were also composed of numerous smaller inclusions under different stages of development or formation. It appeared that these larger ones were formed following fusion and conglomeration of small ones. A further study to elucidate pathogenesis and mechanism of formation of these inclusions is of interest. The nature of these soluble C₆₀ induced vacuoles and inclusions was not determined but was believed to be some component of the compound. It was believed that the soluble C₆₀, i.e., FC₄S, was taken up following the glomerular filtration, into cells by endocytosis, followed by fusion of endocytic vesicle with phagosomes. Whether these phagolysosomal complexes represent C₆₀ component or C₆₀ binding with blood components needs further investigation. Based on these preliminary examinations, FC₄S-induced phagolysosomal nephropathy appeared to differ

somewhat from that of the radiocontrast media-induced lysosome-overload nephropathy (3,7,8) or from other materials, such as glucose and similar chemicals (9), and gentamicin aminoglycoside antibiotics induced nephrosis (10). These compounds each induces morphologically some different form phagolysosomes, and the pathogenesis and mechanism lysosomal inclusions formation are differently involved. It was quite a characteristic inclusion complex observed in the FC4S-treated rat kidney.

The test compound was a water-soluble fullerene derivative (6). The original mother compound was a water-insoluble caged fullerene molecule, i.e., C₆₀ that exhibits high reactive towards organic radicals additions (11,12). To facilitate their medical and therapeutic applications as free radical removers or antioxidants in biological systems, conversion of hydrophobic C₆₀ into its water-soluble derivatives has been a primary research target for many investigators. Several water-soluble fullerene derivatives have been synthesized by Chiang and associates (6,13,14) and are demonstrated to scavenge oxygen radicals *in vitro*. The present compound is one of the synthesized water-soluble C₆₀ that is a polyalkylsulfonated C₆₀, the C₆₀ attaching with 4~6 sodium butyl sulfonate moieties, i.e., C₆₀ [(CH₂)₄ SO₃ Na]_{4~6}, or FC4S. FC4S exhibits high solubility in water and electron affinity better than the water-soluble polyhydroxylated C₆₀, i.e., fulleranol I or C₆₀ (OH)₁₈ (6).

In the present study acute tubular necrosis or nephrosis (ATN) of kidney was observed in the LD₅₀ acute death rats. This ATN observed in the dead rats might be a result of nonspecific system-toxic effect but in the surviving rats was not. ATN is a condition in which tubular degeneration and necrosis are primary process and is an important cause of acute renal failure (15). ATN can be divided into ischemic and nephrotoxic based on the principal causes of ATN. Ischemic ATN is preceded by hypertensive episode (shock) causing severe renal failure. The histological patterns are focal tubular necrosis particularly proximal tubules. Nephrotoxic ATN results from ingestion, injection, or inhalation of a toxic agent which directly damages the tubular cells. Nephrotoxic ATN can be differentiated from ischemic changes because the basement membrane and distal tubular segments are spared. Necrotic changes are most prominent in the proximal convoluted tubules. Nephrotoxicants, as mentioned above may include heavy metals, organic solvents, antibiotics, mushroom toxins, ethylene glycol and chloroform, etc.

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Comparative Pathology Case 84

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Clinical History: A 42-year-old male Taiwanese suffered from repeated episodes of acute urinary retention in recent weeks, and received catheterization twice at emergency service of Cathay General Hospital. He had history of urolithiasis for many years and cystolithotripsy was performed one year ago in Cathay General Hospital. KUB showed opaque stones in both kidneys, spina bifida of S₁ and possibly a right ureteral stone. Intravenous pyelography revealed a left renal stone and multiple calcifications and impaired excretory function of right kidney. Urinalysis was unremarkable. Cystoscopic examination disclosed an intravesical papillary-like lesion located at the bladder trigone near the orifice of right ureter. Biopsy specimen was taken and sent for pathological evaluation.

Diagnosis: Nephrogenic adenoma

Synonyms: Nephrogenic metaplasia; adenomatous metaplasia; adenomatoid metaplasia; tubulo-papillary adenoma

Gross Findings: The specimen submitted consists of two tissue fragments measuring up to 0.4×0.2×0.2 cm in size fixed in formalin. Grossly, they are grayish and elastic.

Histopathological Findings: Microscopically, the section of a well-oriented urinary mucosa shows many papillary fronds with broad inflamed and focally edematous fibrovascular core lined by single layer of cuboidal to columnar cells with eosinophilic cytoplasm. At the base of the papillary fronds, in the lamina propria and occasionally inside the fronds, there are numerous aggregated or isolated tubules lined by flat to cuboidal cells with eosinophilic cytoplasm and focally intracytoplasmic mucin. Moderate interstitial inflammatory infiltrate, including lymphoplasma cells, neutrophils and eosinophils, and scattered foci of calcification at the base of fronds are also noted. Neither increased mitotic activity nor cellular atypia is seen in the lining epithelial cells. The above histological picture is consistent with nephrogenic adenoma.

Histochemical and Immunohistochemical Findings: Histochemical study shows mucin and PAS positive material in the dilated tubules. Immunohistochemical study reveals positive diffuse cytoplasmic staining of the tubulo-papillary lining cells for cytokeratin and positive staining of interstitial stromal cells for vimentin. The prostate specific antigen and carcinoembryonic antigen are negative.

Discussion:

Nephrogenic adenoma (NA) is an uncommon, benign lesion of the urothelial-lined organs from the renal pelvis to the urethra. It was first described in 1949 by Davis; the name nephrogenic adenoma was given a year later by Friedman and Kuhlbeck in a report of eight cases on the basis of striking resemblance to the developing renal tubules and its possible neoplastic potential. More than 75% of cases of NA occur primarily in the bladder, the urethra is involved in 10-15% of cases and, less frequently, the ureter and renal pelvis. In the urethra, NA occurs in the bulbous or prostatic portion and may also occur in a urethral diverticulum. About 90% of patients with NA are adults with a 2:1 male predominance, but there is a 3:1 female predominance of NA among children, almost exclusively in bladder. The patients range in age from 4 to 83 years (mean 41 years). The most common associated conditions include previous surgery (61%), or trauma (9%), infection, calculi (14%), or a history of renal transplant (8%). About two thirds are smaller than 1 cm in diameter, 25% are from 1 to 4 cm in diameter and only 10% are larger. In less than 20% of cases, there are multiple lesions, which rarely include diffuse involvement of the bladder. The lesion is discovered at the time of cystoscopy or is an incidental microscopic finding in about 20% of patients. The signs and symptoms in the remainder of the patients are non-specific, and include hematuria, dysuria, frequency, urgency, and suprapubic and flank pain.

Cystoscopically, NA are papillary (56%), polypoid (10%) or sessile (34%).

Microscopically, NA displays tubular, cystic, polypoid-papillary and diffuse patterns. The most common architecture is tubular (present in 96% of cases). The tubules are typically small and round structures lined by cuboidal epithelium, but occasionally are elongated and solid. Sometimes, they are surrounded by a prominent basement membrane. Cystic dilatation of the tubules is common (present in 72% of cases) and may predominate. Polypoid-papillary structures are present in 65% of cases. Edematous polyps are more common than delicate papillae, which are present in only 10% of cases. Focal solid growth is uncommon.

Most tubules, cysts and papillae have cuboidal to low columnar epithelium with scant cytoplasm, but epithelium with abundant clear cytoplasm is seen in 40% of cases. While hobnail cells focally line the tubules and cysts in 70% of cases, they rarely are predominant. Larger cysts may be lined by flat epithelium and a small amount of mucin may be found in the epithelial cells. Glycogen is present in some cells in 10% to 15% of cases. The nuclei are regular and round, and atypia is rare, usually of degenerative nature. Mitotic figures are absent or rare. NA is often associated with chronic cystitis, which may obscure it. Rarely, it is associated with stromal calcification, squamous metaplasia, or cystitis glandularis.

Ultrastructural and lectin-binding studies reveal some similarities between embryonic renal tubules and NA; however, an embryonic origin remains unproved. Most investigators currently favor a metaplastic origin based on the wide age, site distribution, close association with trauma or inflammation, and evidence of transition from urothelium to NA. Some investigators have suggested that NA is a precursor or a benign counterpart to clear cell

carcinoma in the genitourinary tract. Although there have been a few reported cases of NA coexisting with a clear cell adenocarcinoma, a direct relationship between the two has not been proven. NA can recur following conservative therapy, but in no case is it associated with unequivocal malignant change. The current consensus is that NA is not a premalignant lesion.

NA has a number of features that may cause confusion with bladder carcinoma. Tiny mucin-filled tubules apparently lined by a single cell with a compressed nucleus may resemble signet-ring cells. The irregular disposition of the tubules may simulate invasive adenocarcinoma, especially when the tubules are among the fibers of the muscularis mucosae. Hobnail cells may bring to mind clear cell carcinoma, which shares architectural features of tubular, cystic and papillary structures with NA. In a few cases of NA, papillae are the predominant feature and may cause diagnostic difficulties with other papillary lesions of bladder, such as urothelial carcinoma and papillary cystitis. Recognition of a single layer of cuboidal epithelium covering the papillae of NA differentiates it from these lesions, which are covered by multilayered urothelium.

Furthermore, the other differential diagnosis of NA include prostatic adenocarcinoma and clear cell carcinoma of the urethra. The differentiation of NA from adenocarcinoma is generally not difficult, but NA occurring in the urethra merits special discussion. In this location it may be found incidentally in TUR-P specimens. The small, closely packed tubules of NA may closely mimic adenocarcinoma of the prostate. Usually the lack of nuclear atypia or nucleoli and the typical edematous stroma seen in NA are sufficient to distinguish it from prostatic adenocarcinoma, but immunohistochemical studies for PAP and PSA are useful to separate it from prostatic adenocarcinoma on difficult cases. Intracytoplasmic mucin positivity suggests NA, since the mucin in prostatic adenocarcinoma tends to be intraluminal. NA can easily be distinguished from clear cell carcinoma as the latter shows significant nuclear pleomorphism and paucity of mitotic figures. In fact, recognition of more than a sporadic mitotic figure in a lesion considered initially to be nephrogenic adenoma should raise the consideration of a carcinoma that resembles nephrogenic adenoma, either clear cell adenocarcinoma or transitional cell carcinoma with small tubular differentiation

Diagnostic Criteria:

1. Clinical history of surgery, trauma, calculi, renal transplant, inflammation, or other causes of chronic irritation of urinary tract.
2. Aggregates or isolated small tubules lined by flat to cuboidal cells with occasional papillary fronds formation and cystic dilatation.
3. Absence of cellular atypia and significant mitotic activity

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Comparative Pathology Case 85

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Clinical History: A 4-year-old female, unknown breed, hunting dog has showed anorexia about one month period and was treated for ten days at a local veterinary hospital.

Diagnosis: Renal amyloidosis

Gross Findings: Necropsy was performed by the veterinarians at Miaoli Livestock Disease Control Center. The gross lesions were described as followings: emaciated body, green-blue patches (approximately 2-3 cm in size) over the liver, peritonium, and lung. The urinary bladder and gastric mucosa were severely congested. The heart was dull-round in appearance. The submitted formalin-fixed small slices of kidney tissue showed depressions of capsular surface, pale-yellowish cortex with tiny opaques and indistinct cortico-medullary junction.

Histopathological Findings: Microscopically, all the glomeruli became extremely enlarged were involved in homogenous and hyaline deposition. Amyloid was also detected in the tubular basement membranes, blood vessels, and interstitial tissue. The renal tubules showed variably atrophied, dilated or degenerated. Multifocal aggregates of plasma cells and lymphocytes were present in the interstitium of the cortex. In addition, peritubular, periglomerular, and glomerular mineralization and proteinaceous fluid in the renal tubules were observed. Besides kidney, the spleen was other involved organ.

Histochemistry Results: Both Congo red and Leb's crystal violet method confirmed amyloid substance in the renal tissue, particularly the glomeruli. Von kossa for mineralized salts and Masson's trichrome stain for interstitial fibrosis confirmed the histologic lesions.

Immunocytochemistry Results: Most of the glomeruli and amyloid-deposited tissue were stained positively for amyloid AA, but negatively for β -amyloid.

Discussion: Amyloidosis is the disease process characterized by the extracellular deposition of approximately 10 nm fibrillar protein with a β -pleated sheet conformation in the basement membranes, vessels, and stromal connective tissue of varying organs and body tissues. Amyloid protein is Congo red binding and apple-green in polarized light. The disease

has been identified in man, birds and various mammals and shares many clinical and pathological similarities. In a respective study of animal amyloidosis at Department of Pathobiology, Pig Research Institute, Taiwan, the disease has been observed in dogs, mice and birds. The most affected organs include the kidney, liver and spleen. In the kidney, amyloidosis in the dogs is characterized by generalized and progressive glomerular destruction, proteinuria and leading to irreversible renal failure. It is common in older dogs, with almost 85% being 7 years of age or older, and females were affected than males. Common clinical signs were progressive PU/PD and nocturia. If the animal is in renal failure, typical signs including depression, anorexia, lethargy, vomiting, dehydration, pale mucous membrane and weight loss may be observed. In addition, an unexpected high incidence of thromboembolic tendency has been observed at necropsy in dogs with renal amyloidosis. No laboratory tests can specifically indicate the presence of renal amyloidosis in the animal species, although persistent proteinuria is a consistent finding, it is only an indication of generalized glomerular disease. However, a recent finding indicated that decreased excretion of urine glycosaminoglycans may serve as a marker in human renal amyloidosis. Pathologically, the glomeruli are the usual and most important site of deposition, but vessel walls and surrounding tubules are also commonly involved. In cats with renal amyloidosis, however, medullary amyloidosis is predominant and more consistently than glomerular amyloidosis. Renal amyloidosis in the dogs occurs in association with chronic infectious, inflammation and neoplastic diseases, in many instances no predisposing diseases can be detected. Immunocytochemical studies demonstrate the presence of amyloid A component, a presumed degradative product of SAA, the presented case is classified as reactive (secondary) amyloidosis, but no obvious diseases have been attributed. By amino acid sequence or on the basis of amino acid composition, protein AA has been identified in man, monkey, mouse, guinea pig, duck, mink, dog, cattle, and hamster. Currently, the precise etiology and pathogenesis of amyloidosis are still unknown, spontaneous canine amyloidosis and human reactive amyloidosis show many similarities in clinical, laboratory, pathological, and immunocytochemical aspects, therefore, canine model may aid in defining mechanism of human amyloid pathogenesis (Table 1).

Table 1. Comparisons of human and canine reactive renal amyloidosis

	Human	Canine
Age	median age (25~64 y/o)*	6 years or older
Sex	males predominant*	females predominant
Breed	not available	Beagles, Collie, Walker Hounds
Clinical signs	nephrotic syndrome, renal vein thrombosis with auria	PU/PD, nocturia, renal failure, and thrombosis
Laboratory tests	proteinuria, azotemia, urine glycosaminoglycans	proteinuria, azotemia
Pathology	amyloid deposits in the glomeruli, BV, and tubular basement membranes	amyloid deposits in the glomeruli, BV, and tubular basement membranes
Histochemistry	Congo red	Congo red
Immunocytochemistry	Amyloid A positive	Amyloid A positive
Predisposing factors	RA, TB, paraplegia, multiple myeloma, bronchiectasis, leprosy, SLE, Hodgkin's disease, dermatomyositis, syphilis, osteomyelitis, familial Mediterranean fever	SLE, cyclic neutropenia, insulin infusion, neoplasia

*:Only for AL (primary or myeloma related) amyloidosispatients, AA (secondary) amyloidosis was unknown (or broad ranges)

Diagnostic Criteria:

1. Renal biopsy
2. Lugol's iodine stains amyloid brown on fresh slices of affected tissue
3. Congo red stains amyloid orange and has birefringence when viewed with polarized light.
4. Electron microscopic features.
5. Immunohistochemistry.

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Comparative Pathology Case 86

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Clinical History: A 63-year-old man with diabetes mellitus for 6 years experienced exertional dyspnea, oliguria, and bilateral leg edema since Jan. 1992. Chronic renal insufficiency with congestive heart failure and urinary tract infection was diagnosed at another hospital 2 months later. Deterioration of the renal function was noted despite of medical treatment. Persistent nausea, anorexia, general weakness and progressive drowsiness led to admission to our hospital on Apr 29. Generalized eczema with desquamation, macroglossia, uremia, anemia, hypercalcemia, A-V block on ECG, and elevated serum LDH level were noted. Further investigations confirmed the diagnosis. Unfortunately, the patient developed UGI bleeding and pneumonia. He was found apneic after an episode of vomiting and expired despite vigorous resuscitation on May 23, 1992. Autopsy was performed.

Diagnosis: Multiple myeloma with systemic amyloidosis

Gross Findings: Bilateral kidneys appeared brownish and waxy, with normal sizes and slightly decreased weight (100 gm each). Biventricular hypertrophy of the heart (weight=1100 gm), multiple punch-out lesions in the skull bone, hepatomegaly (weight=1580 gm), hemorrhagic gastric mucosa, multiple pneumonic patches and fibrinous pericarditis were noted.

Histopathological Findings: It showed classic multiple myeloma composed mainly of mature plasma cells with a few plasmablasts involving vertebrae, ribs, skull bones and pulmonary hilar lymph nodes. Immunohistochemistry studies revealed $\lambda(+)$, $\kappa(-)$. The kidneys showed myeloma cast nephropathy characterized by PAS (-) proteinaceous casts in the distal tubules and collecting ducts with multinucleated giant cell reaction. Marked tubular atrophy, moderate glomerulosclerosis and broadening of the interstitium were noted. Homogeneous pinkish amyloid deposits were found around the Bence Jones casts, renal tubules, in the interstitium and vascular walls of the kidneys, as well as in the other sites such as the heart, liver, GI tract, pancreas, thyroid gland, adrenal glands, etc. Congo red stain disclosed greenish birefringence under polarized light. Immunohistochemical study showed light chain reactivity in the myeloma casts but not in the glomeruli.

Discussion: Over one century ago, Virchow first used the term, *amyloid*, meaning “starch-like”, to describe the deposits he observed in amyloidotic tissue stained with iodine solutions. It is now apparent that amyloidosis is not one disease but a common manifestation

of diverse diseases, characterized by extracellular accumulation of fibrillary proteins, most of which are 7- to 10-nm thick and are arranged mainly in β -pleated sheets. Approximately 20 different proteins are responsible for amyloid deposits, and a classification of the various amyloids according to protein type has been given by the WHO-IUIS Nomenclature Sub-Committee. On the way of understanding the events and factors involved in amyloidogenesis, researchers have had some achievement. To our knowledge, AL-type amyloids, which are the major constituent of primary or myeloma-associated amyloidosis, can be considered as the result of abnormal dimerization of the light chain fragment that contains variable region (V_L), followed by the interaction of these dimers to form filaments and, finally, between filaments to form fibers. The extreme variability of light chain metabolites implies the complex microenvironment existing in different tissues. In this case, we demonstrate the variable casts, crystals and amyloids in different locations, and compare the findings with reports in the literature. The biochemical aspects of amyloidogenesis are also briefly discussed.

Therapy for myeloma-associated amyloidosis has been unsatisfactory although few reports claimed success. More needs to be elucidated to accomplish successful treatment of amyloidosis.

Diagnostic Criteria:

1. serum/urine M component (+).
2. multiple osteolytic lesions.
3. plasmacytosis (>10%) in bone marrow.
4. positive Congo red stain.

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Comparative Pathology Case 87

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Clinical History: A 78-year-old female, on regular hemodialysis trice per week for ten years, presented with a palpable mass over right flank to the hospital. Abdominal computed tomography revealed an enlarged right kidney (16.0×12.0×6.0 cm). Right nephrectomy was performed.

Diagnosis: Squamous cell carcinoma of renal pelvis and calyces with extension to the ureter.

Gross Findings: The entire specimen, including kidney and its associated capsule, adipose tissues, and ureter, measures 16.0×12.0×6.0 cm. It is bisected and the renal capsule is stripped off. The pyelocalyceal system is markedly dilated with brownish soft contents and covered with multifocal whitish irregular excrescences. The renal cortex is compressed and measures 0.1 to 0.5 cm in thickness. The renal medulla is flattened. The cortico-medullary junctions are indistinct. No calculi are observed.

Histopathological Findings: The neoplasm has extensively involved the surface of dilated pelvis and calyces with focal invasion into the overlying renal parenchyma and extension to the ureter. It is comprised of pleomorphic polygonal cells with high N/C ratio, hyperchromatic nuclei, and enlarged nucleoli. Intercellular bridges are occasionally found. Keratin pearls are not observed. The renal parenchyma shows diffuse atrophy with focal lymphoplasmacytic infiltrates in the interstitium. The tubules are focally dilated and contain proteinaceous inspissated materials (thyroidization).

Discussion: Transitional cell carcinoma accounts for 91% of carcinoma of renal pelvis, with squamous cell carcinoma and adenocarcinoma, 8% and below 1%, respectively. Squamous carcinoma of the renal pelvis was diagnosed in only 11 of 2166 renal tumors (0.5%) seen over a twenty-seven-year period in a large-scale study (Ref. 2). Pelvic squamous cell carcinoma are more common in men than in women and are mostly seen in the sixth and seventh decades. There may be a causal relation to long-standing pyelonephritis, renal stones, and squamous metaplasia, but not apparently to chemical dye exposure, Balkan nephropathy, or phenacetin abuse. The process is assumed to begin with urothelial metaplasia resulting from a reaction to chronic irritation, which leads to dedifferentiation, dysplasia and ultimately squamous cell carcinoma or adenocarcinoma. Massive urothelial condyloma acuminatum with a long history is also mentioned as a possible etiologic factor in sporadic cases reports (Ref. 11).

The results of nuclear deoxyribonucleic acid ploidy studied by flow cytometry

significantly correlated with histological grade and tumor stage (Ref. 5). Almost all tumors were histologically high grade; among the patients with high grade tumors, ploidy analysis distinguish fair and poor prognosis groups. Pathological stage was the dominant factor in prognosis. There is no clear statistical evidence that ploidy analysis provides important prognostic information independent of stage and grade for patients with squamous cell carcinoma of the renal pelvis.

The combination of insidious onset and an indolent clinical course (median: 5 months) resulted in all patients having extensive local infiltration at diagnosis. The prognosis for pelvic squamous cell carcinoma is poor. Early diagnosis and surgical treatment before the tumor has extended beyond the capsule offer the best hope for cure. The treatment of choice is radical nephrectomy followed by adjuvant chemotherapy.

Diagnostic Criteria: Nests and sheets of polygonal cells with intercellular bridges and varying degrees of keratin formation.

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Comparative Pathology Case 88

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Clinical History: A 43-year-old female was noticed to have a dark red mass protruding from the urethral meatus. There showed a long pedicle within the urethra. She had urinary frequency, dysuria, burning sensation on micturition for one month. Transurethral resection was done. The specimen submitted was a grayish black polypoid lesion of 6×5×3.5 cm and weighed 30 gm.

Diagnosis: Fibroepithelial polyp of the ureter

Gross Findings: A grayish black polypoid lesion of 6×5×3.5 cm and 30 gm.

Histopathological Findings: Fibroepithelial polyp with fibrous stroma exhibiting severe congestion, hemorrhage, and edema. The surface is eroded and lined focally by urothelium.

Discussion: Benign tumors of the urinary tract are rare. While fibroepithelial polyps are the commonest benign tumor-like masses of the renal pelvis and ureter. They are mesodermal in origin and consist of a thick fibrous stalk covered by a layer of normal transitional epithelium. They are commonly present in young adults with gross painless hematuria and intravenous urography often demonstrates a polypoid filling defect which rarely causes upper tract obstruction.

Diagnostic Criteria: Benign polypoid tumor with fibrous stroma and lined by transitional epithelium.

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6.Comparative Pathology Case 89

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Clinical History: There was a goose farm in the central of Taiwan. The farm raised about 1,500 geese, divided into 2 groups, 750 3-month-old geese and 750 3-month-old goslings. About 2 weeks ago the geese showed signs of respiratory symptoms. The gooseherd tried to treat them with many kinds of antibiotic drugs such as sulfa drugs etc. for 10 days. But the gooseherd didn't really remember how many kinds of drugs and the dosage he had used. The illness of the farm didn't improve, so the gooseherd took 3 dead geese to National Chung-Hsing University Veterinary Teaching Hospital for pathological diagnosis. After necropsy the chalk white urate crystals covered on thoracoabdominal viscera, synovial membranes of the joints and the tendon sheaths and the polyserositis were remarkable lesions.

Diagnosis: 1. Severe visceral gout due to kidney damaged
2. Infectious serositis

Gross Findings: Large amount of chalk white crystals covered on thoracoabdominal viscera (including: liver, spleen, gonad, intestine, gizzard, lung, and air sacs etc.). The pericardium and epicardium (the crystals packed and adhered pericardial sac) were also involved. All of the joint cavities (including: toes, phalangeal, hip, elbow, and shoulder etc.) were deposited with urate crystals. Some parts of serosal surface of the lung lobes and air sac were covered by fibrinous fluid.

Histopathological Findings: Most parts of the proximal convoluted tubules were degenerated and necrotic. Some parts of the necrotic tubules were dilated and accumulated with urate crystal shadow (star-shape or irregular shape). Collecting ducts and distal tubules still remained normal. Small amounts of urate crystals were observed in the ureters. The urate crystals on the serosal surfaces of the heart, liver, spleen, intestine, and joint cavities were also detected. Large amounts of inflammatory cells and fibrin covered on the pleura and the coliform granuloma were also found.

Discussion: The pathomechanism was that the affected geese's kidneys were damaged by some kinds of antibiotics. Most of the proximal convoluted tubules were necrotic and disturbed the excretion of urate, this resulted in the production of visceral gout.

It is most important to stress at onset that visceral gout is merely the sequel to renal failure and not a disease entity in itself. In the uricotelic bird, where the type of waste product of protein metabolism is uric acid, a loss of renal tubular function rapidly leads to

hyperuricaemia and consequently visceral gout, in which a deposition of urate crystals on the serosal surfaces of the thoracoabdominal viscera, the synovial membranes of the joints, and tendon sheaths were obviously seen. The loss of tubular function may be due to primary tubular damage or to back pressure following obstruction of the ureter and its branches.

Differential diagnosis:

Gross and histopathological changes of the kidneys
in the various renal disease of the fowl

- Visceral Gout:
 1. Gross: Various, Kidneys often contain urates
 2. Histopathology: Non-specific; depend on primary disease. Often urate tophi, impaction of ureters, ureter branches and collecting duct (CD)
 3. Comment: This is evidence of renal failure and not a disease entity

- Vitamin A deficiency:
 1. Gross: Dilatation and impaction of ureters. Urates in kidney substance
 2. Histopathology: Dilatation of collecting duct system. Metaplasia of ureter and CD epithelium
 3. Comment: Visceral gout

- Sodium intoxication: (Na:K imbalance)
 1. Gross: Dilatation and impaction of ureters. Heavy urate deposits often present on kidney surface below peritoneum.
 2. Histopathology: tubular degeneration and urate accumulation. Some tophi
 3. Comment: Visceral gout may be present

- Calcium nephropathy:
 1. Gross: In chronic stage, renal atrophy, distension of ureters
 2. Histopathology: Interstitial fibrosis, tubular dilatation no calcification with reasonable diets
 3. Comment: Visceral gout may be present

- Urolithiasis:
 1. Gross: Asymmetrical renal atrophy, ureter stone distension of ureters
 2. Histopathology: Tubular dilatation sometimes. Degeneration and/or inflammation, interstitial fibrosis
 3. Comment: In laying bird. Visceral gout may be present

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Comparative Pathology Case 90

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Clinical History: A 2-year-7-month old boy was admitted at Taipei Municipal Jen-Ai Hospital on June 12, 1983 due to a big abdominal mass. The big mass had persisted for one year. On his first admission, a big solid mass was found and located at right abdominal space measuring 15×13 cm in size. After a serial examination, the mass surely arose from the right kidney and resected on June 21, 1983. Post-operative chemotherapy (actinomycin D, vincristine, cyclophosphamide) was given, but four months chemotherapy ended, abdominal distension developed. Radiotherapy (totally 1500 rads) was added. The patient was well still a recurrence 14 months later (4-year-1-month old). The second admission on Jan 10, 1985 for resected the recurrent tumor. After the second operation, the child had received an additional 17 courses of chemotherapy and then he had 3 years of remission. At 7-year-1-month of age, liver metastasis was found and the patient died one month later. This was four years and six months after the first operation. No evidence of bone metastasis was detected.

Diagnosis: Clear cell sarcoma of kidney

Gross Findings: The resected kidney measured 18×11×8 cm in size and 850 gm in weight. It was markedly compressed by the tumor and the surface was lobulated and focally hemorrhagic. The tumor, measuring 17×11×8 cm in size, occupied a major part of the kidney, seeming to arise from medulla of the kidney; it was rather well defined. The calyces and the pelvis had disappeared, and only a small rim of renal tissue remained in the lower pole. Lymph node metastasis and Gerota's capsule invasion were not found. The second resected recurrent retroperitoneal tumor (about 650 gm) was soft, friable and covered by whitish membranous capsule. The tumor was made up of myxomatous tissue with focal hemorrhage. No evidence of cyst, bone nor cartilage was seen.

Histopathological Findings: The tumor was composed of medium-size, oval or spindle-shaped cells with clear cytoplasm and centrally located small round benign-looking nuclei with finely dispersed chromatin. The tumor cells characteristically were arranged into ill-defined solid alveolar groups by abundant arborizing and branching capillaries supported by bundles of spindle-cell stroma. Regular trabecular arrangement was observed occasionally. High cellularity foci separated only by capillaries without supporting stroma and small cystic degeneration could be seen occasionally. Capsular invasion and rare mitosis were noted. Neither focal necrosis nor nephroblastic element was found.

Mucin, PAS and alcian blue stains were all negative and no neurosecretory granule was demonstrated by chromogranin stain. In immunocytochemical stains, P⁵³, desmin, EMA, myocin, and myoglobin were all negative but vimentin and cytokeratin were positive in some of clear cells and the arborizing capillaries. The recurrent tumor was still made up of clear cells, but revealed marked myxomatous degeneration intermixed with patches of fibrosis and capillaries. Histochemical and immunocytochemical stains showed the same reactions as in the original tumor.

- Diagnostic Criteria:**
1. unilateral and unicentric
 2. infiltrative border between the clear cell sarcoma and the surrounding renal parenchyma
 3. renal tubules frequently surrounded by sarcoma
 4. branching or arborizing capillaries
 5. neoplastic cell: clear cytoplasm and round-oval nuclei with finely dispersed chromatin
 6. absence of blastema, cartilage, muscle

Discussion: Clear cell sarcoma of the kidney (CCSK), a name first used by Beckwith and Palmmer in 1978 (1), is the same tumor reported by Kidd in 1970 (2) “sarcomas of the predilection to metastasize to bone” CCSK had also been called “bone-metastasizing renal tumor of children (3)”. The incidence of CCSK is about 4% in total renal tumors of children in NWTs (4). The age distribution of the patients with CCSK ranged from a few days (5) to 15 years old (6) with a mean of 36 months (7) and peak at 2.5 years old (8). The male to female ratio was about 2:1 (8). The most common clinical signs of patients with CCSK were abdominal mass and hematuria (9). More than 50 percent of the tumors weighed over 500 gm (4,9), but the size of the tumor did not correlate with the stage on prognosis (4). There might be a predilection (4,9) for the right kidney or no difference between them (10), and no report showed bilateral involvement by CCSK. The frequency of bone metastasis was documented from 17% to 60% (3,11,12). The locations of metastasis in order of frequency were bone, lung, abdominal cavity (7). Grossly, CCSK presents as a well-defined tumor mass, mostly located in the medullary or hilar region of the kidney (7). The cut surface is firm and homogeneous gray-white, sometimes with small cysts. It is seen to infiltrate the adjacent renal tissue, leaving scattered residual renal tubular structures within the sarcoma. The tumor cells are monomorphous and have clear cytoplasm. The nuclei are oval-to-round in shape with fine and evenly distributed chromatin. The cell border is indistinct and mitosis is spare. There are many delicate interlacing networks of fibrovascular septa. The essential microscopic feature of CCSK is the clear cells with abundant and evenly distributed fibrovascular stroma, creating an alveolar or occasionally trabecular pattern. The clear cytoplasm cannot be stained with PAS, toluidine blue, old red O and mucin. Under the EM examination, the cells contain little glycogen and only rarely cytoplasmic fat. The clear appearance is given by the mosaic

arrangement of the cells that may include pools of abundant pale extracellular matrix.

Condensation of microfilaments following formalin fixation may also be responsible for this light microscopic appearance (13).

Although variants of CCSK exist rarely, the type most commonly encountered is that with progressive proliferation of the spindle cells in the septa (8). This may lead to confusion with congenital mesoblastic nephroma (CMN) or with stromal components of Wilms' tumor. The characteristic interlacing bundles of small hyperchromatic spindle cells are commonly seen in CMN (8). This is the main point in distinguishing between CMN and CCSK. If blastemal aggregation, is present and/or three-cell line differentiation, then the diagnosis will not be CCSK. On the other hand, fine chromatin patterns in nuclei, sclerotic or hyalinized stroma, and entrapped renal elements favor for CCSK (8) prognosis for CCSK is poor, appearing to be worse than for ordinary typical Wilms' tumor, showing two-year survival rate about 50% (13). The series followed up by Sotelo-Avila et al (9), showed similar results, with only 8 out of 21 cases of CCSK surviving 1-4 years (9). As for histogenesis of CCSK, the most prevalent hypothesis has appeared to be that the tumor originated from metanephric blastema (3,14). But, based on ultrastructural features, Hass and associates proposed the theory of primitive mesenchymal cell origin (13). However epithelial differentiation in CCSK cell lines has been shown by Ishii et al (15).

Immunocytochemical stains have been employed to clarify the pathogenesis of CCSK, but thus far without conclusive event. Even though vimentin and cytokeratin, as in this case, had been identified in cytoplasm (16), positive for alfa-1 antichymotrypsin (AACT) and negative for uroepithelial antigen 2,3 and 4 has also report (17).

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Comparative Pathology Case 91

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Clinical History: Between March 1996 and March 1997, three male orange-rumped agoutis died in their exhibits in the Taipei Zoo. Gross examination revealed similar pathological changes, including severe mineralization in the heart and kidney. These animals were kept in the nocturnal house where they had limited access to light exposure and vitamin D was supplied as a dietary additive.

Diagnosis: Hypervitaminosis D

Gross Findings: The size of the kidney of these dead animals were normal or mildly swollen, with multiple white pinpoint spots overspreading the surface. Zones of small white granular, gritty lesions were present in the area at the cortico-medullary junction. White scrappy patches were disseminated on the surface of both the endocardium and epicardium, as well as in myocardium. Similar lesions were also noticed in the pyloric region of the stomach in one agouti. In another agouti, the surface of the aorta was rough and the wall was tough as a solid pipe.

Histopathological Findings: Zonary mineralization was present in the basement membrane of the glomeruli and the renal tubules. Lesions of renal tubules include tubular distention and distortion, tubular epithelium sloughing, degeneration and necrosis, and accumulation of proteinous substances in the lumen, while some of the Bowman's spaces were enlarged. Signs of chronic, mild to moderate, diffuse, tubulointerstitial nephritis were seen in one of the agoutis, including longitudinal interstitial fibrosis and inflammatory cell infiltration predominated by mononuclear cells which were mainly lymphocytes and plasma cells. There were severe, multifocal to coalescent mineralization, necrosis, and fibrosis in the myocardium.

Annular mineralization occurred in the tunica media of the aorta and other large and medium-sized arteries in the heart, spleen, tongue, stomach, intestines and lung, while the endothelium remained intact. The mineralization seen in the alimentary tract was mainly localized in the muscle layer of the wall and the tunica media of small to medium-sized arteries in various regions, without involving the mucosa.

Special Stain: Von kossa: The positively stained calcified lesions appeared as tenuous bands around the basement membrane of the glomeruli and renal tubules. Medial calcification could be found in the aorta and small to large-sized arteries of the heart, spleen, tongue, stomach, intestines, and lung. Multifocal to coalescent severe calcium deposits were also seen in the necrotic lesions of the heart.

Serum Biochemistry and Hematology:

Item (Units)	Ref.	Date	1	2	3	4	5	6	7	8	9	10
Sex			F	F	F	F	F	F	F	F	F	M
PCV (%)	40.8-53.0	4/14	52.1	50.7	54.2	60.0	42.7	65.6	42.5	44.7	48.3	51.4
Ca (mg/dl)	8.0-10.8	4/14	11.9	11.9	12.2	10.7	12.0	11.3	12.6	11.6	10.9	11.3
		9/12	9.3	10.2	8.7	9.4	9	9.5	10.2	10.1	10.2	9.1
P (mg/dl)	2.6-5.0	4/14	8.8	7.0	5.8	6.0	8.1	7.8	6.4	8.3	5.5	8.3
		9/12	3.1	5.2	5.5	2.6	3.1	4.3	6.6	5.2	5.4	3.1

Radiography: Radiological examination was done in the remaining agoutis, but no evidence of mineralization or bone lysis was seen in the thoracic and abdominal viscera and bone, respectively.

Discussion: Hypervitaminosis D (HD) results in the elevation of serum calcium level and subsequent mineralization of soft tissues, including the kidney, which in turn leads to renal failure. The etiologies for HD include dietary vitamin D toxicosis and calcinogenic plant toxicosis. The former may occur acutely as it does in dogs exposed to cholecalciferol-containing rodenticide or from long-term intake of rations containing excess Vitamin D fortification as in the present case. The latter condition can ensue from ingestion of calcinogenic plants, which contain the active metabolite of vitamin D₃ (1,25-dihydroxycholecalciferol, 1,25-D₃) or its glycoside, such as *Cestrum diurnum*, *Trisetum flavescens*, *Solanum malacoxylon* and *S. torvum*. Different names have been given in various areas of the world, including “Manchester wasting disease” in Jamaica, “enzootic calcosinosis” in Europe, “naahelu disease” in Hawaii, “enteque seco” in Argentina, and “espichamento” in Brazil.

Pathophysiologic features of hypervitaminosis D include hypercalcemia, hypercalciuria, and decreased fecal fat. Hypercalcemia is derived mainly from intestinal calcium absorption and, to a lesser extent, from bone reabsorption and diminished glomerular filtration. The pathological effects of hypercalcemia are compounded by the damaging action of excessive vitamin D on membranes. As a result, mineral deposits are laid down in soft tissues, including basement membranes of the renal tubules, glomeruli, myocardium, arterial wall, and alveolar septa of lung.

Symptoms and clinical signs generally appear 2 to 8 days after acute intoxication with massive doses of vitamin D; conversely, it may take months or even years for sufficient vitamin D accumulation to produce symptoms during chronic intoxication. The manifestations are related to the degree of hypercalcemia and include weakness, fatigue, headache, nausea, vomiting, and diarrhea in the early stages. Polyuria and polydipsia usually develop because hypercalcemia inhibits the action of antidiuretic hormone on the distal tubule. Nephrocalcinosis and metastatic calcifications of the cardiovascular systems, as a result of prolonged hypercalcemia, lead to hypertension, cardiac insufficiency, renal failure, azotemia, and anemia.

The agoutis are kept in the nocturnal house in the Taipei Zoo where light exposure is limited to two hours a day; however, they are actually diurnal animals in nature and acquired nocturnal habit to escape from predators. In order to prevent the possible situation of hypovitaminosis D as a consequence of decreased endogenous synthesis by the skin secondary to the limited light exposure, the agoutis had been given weekly dietary vitamin D supplementation. The necropsy findings, combined with the result of serum biochemical examination on April 14th, revealed elevated serum calcium and phosphorus levels, indicate that the animals may have suffered from hypervitaminosis D due to excessive dietary vitamin D. The supplementary of vitamin D was ceased thereafter, and the biochemistry index returned to normal range when we reexamined the animals in September.

Suspected vitamin D₃ toxicity in pacas and agoutis had been reported by David Kenny et al (1993), describing a suspected nutritional problem that was encountered in mixed-species exhibits containing New World rodents and primates. Three institutions, the Denver Zoological Garden, Cleveland Metropark Zoo, and Roger Williams Park Zoo, experienced a total loss of nine pacas and two orange-rumped agoutis due to extensive soft tissue mineralization. In each case, the rodents were exhibited indoors with New World primates and had access to all food items in the exhibit. Commercial formulations for marmoset and primate diets contain levels of vitamin D₃ which might be toxic to other species, and toxicity in rodents probably develop since they customary eat fallen primate diet from the floor.

Diagnostic Criteria:

1. Extensive mineralization of various tissues, including the kidney, heart, stomach, aorta, and tunica media of large arteries.
2. Elevated serum calcium and phosphorus level.

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