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Long-term outcome of acute renal injury induced by *Aristolochia manshuriensis* Kom in rats

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KEY WORDS *Aristolochia manshuriensis* Kom; nephrotoxicity; acute renal failure; interstitial nephritis; *kidney diseases; neoplasms*

ABSTRACT

AIM: To investigate the long-term functional and morphological changes of the kidney induced by acute intoxication of *Aristolochia manshuriensis* Kom in rats. **METHODS**: Experimental model of acute renal injury was established in the Sprague-Dawley rats with oral administration of decoctions of Chinese herb, *Aristolochia manshuriensis* Kom, at dosages of 50 $g \cdot kg^{-1} \cdot d^{-1}$ and 30 $g \cdot kg^{-1} \cdot d^{-1}$ for 7 consecutive days, and 20 $g \cdot kg^{-1} \cdot d^{-1}$ for 15 consecutive days. Renal function was assayed at months 0 (right after treatment), 1, 3, and 6 of the experiment. Renal histological examination was also performed. **RESULTS**: 1) At month 0, the renal functional changes of acute renal injury included azotemia, low molecular weight proteinuria, glycosuria, hypoosmotic urine, and NAG enzymuria. Histopathological changes showed acute tubular necrosis, predominantly at the corticomedullary junction. 2) At months 1 and 3, the renal function of rats of the experiment was gradually restored and histopathologic examination suggested that the tubular lesions gradually recovered. In HE sections, basophilic deposits were observed in the tubular cytoplasm. And interstitial infiltration of inflammatory cells was not prominent. 3) At months 6, renal preneoplastic lesions, renal tumors, and extrarenal tumors occurred in rats. The occurrence of renal preneoplastic lesions at dosages of 50 $g \cdot kg^{-1} \cdot d^{-1}$, 30 $g \cdot kg^{-1} \cdot d^{-1}$, and 20 $g \cdot kg^{-1} \cdot d^{-1}$ were 100.0 % at all three doses, renal tumors 42.8 %, 25.0 %, and 0 %, respectively, extrarenal tumors 14.4 %, 12.5 %, and 12.5 %, respectively, and systemic tumors 57.2 %, 37.5 %, and 12.5 %, respectively. The occurrence of basophilic deposits, renal preneoplastic lesions, renal tumors, and extrarenal tumors in normal control group was nil. **CONCLUSIONS**: 1) Administration of large dosage of *Aristolochia manshuriensis* Kom induces acute renal failure in rats. 2) The long-term renal function and histopathologic changes of acute renal injury induced by *Aristolochia manshuriensis* Komrecover spontaneously. 3) *Aristolochia manshuriensis* Kom has been proved to be oncogenic for the first time.

INTRODUCTION

Aristolochia manshuriensis Kom, a Chinese herb belonging to *Aristolochiaceae*, is commonly used as a diuretic in traditional Chinese medicine. It has already been reported that individuals develop acute renal failure after ingesting overdose of the herb[1-7]. Now the herb is still widely used and similar cases reported frequently. Meantime, we also observed that patients intoxicated with the herb usually followed a chronic course and eventually developed chronic interstitial nephritis or even went into end stage renal failure. However, systemic clinical and experimental studies have not been reported. In order to study thoroughly the nephrotoxicity of the herb, in our previous work, we have established the experimental model of acute renal injury in the Sprague-Dawley rats with oral administration of decoctions of the Chinese herb and made a preliminary observation of functional and morphological features of acute nephrotoxicity induced by the herb[8]. This report describes the long-term functional and morphological changes of acute renal injury induced by the herb in rats.

MATERIALS AND METHODS

Material *Aristolochia manshuriensis* Kom was

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purchased from Sale Department of Traditional Chinese Medicine and was identified by Prof Ding Lin-Sheng, China Pharmacential University. Decoctions of *Aristolochia manshuriensis* Kom (containing 2 g drogen/mL) were prepared conventionally.

Experimental design Female Sprague-Dawley rats (Grade Ⅱ, Certificate № 99-004) weighing 160-180 g were purchased from Shanghai Experimental Animal Center, Chinese Academy of Sciences. The rats were randomly assigned into four groups. Experimental model of acute renal injury was established with oral administration of decoctions of the Chinese herb, *Aristolochia manshuriensis* Kom. Group A ($n = 40$) and Group B ($n = 30$) were dosed at 50 $g \cdot kg^{-1} \cdot d^{-1}$ and 30 $g \cdot kg^{-1} \cdot d^{-1}$ respectively for 7 consecutive days, and group C ($n = 30$) was dosed at 20 $g \cdot kg^{-1} \cdot d^{-1}$ for 15 consecutive days. Group D (normal control group, $n = 30$) received the same amount of drink water. The animals were allowed free access to food and water during experiment.

Renal function Blood samples and 24-h urine collections were taken for examination prior to sacrifice at months 0 (right after treatment), 1, 3, and 6 of the experiment. Serum urea was determined by enzymatic colorimetric method, serum creatinine by Jaffe's method, urinary activity of *N*-acetyl-beta-*D*-glucosaminidase (NAG) by enzymatic colorimetric method, urinary protein by Buriet method, glucose by hexokinase method, and osmolality by an osmometer. Analyses were performed by the Department of Clinical Biochemistry or Department of Nephrology.

Histology Kidney tissues for histological examination were fixed in 10 % neutral formalin, routinely paraffin embedded, and 4-μm sections were stained in phosphotungstic acid-hematoxylin-eosin or period acid-Schiff (PAS), then examined under light microscop. Von Kossa silver nitrate method was used for demonstration of calcium deposits[9]. Calcium deposits were stained black, nuclei were stained red and other tissues were stained pink.

Statistical analysis The comparison of measurement data was performed by Student's t-test, and the comparison of percentage was performed by Fisher's exact test. Statistical significance was defined as $P < 0.05$. Data was expressed as $\bar{x} \pm s$.

RESULTS

Renal function At month 0 (right after treatment), changes in renal functional parameters in three dosage groups included the increase in serum urea and creatinine, the increase in urine NAG, urine protein and glucose, and the decrease in urine osmolality compared to the normal control group, and exhibited a dose-dependent pattern. The changes were most pronounced in the highest dosage group (group A), statistically very significant ($P < 0.01$) compared to the normal control group. Although the accumulative dosage was markedly less in group B (30 $g \cdot kg^{-1} \cdot d^{-1} \times 7$ d) than in group C (20 $g \cdot kg^{-1} \cdot d^{-1} \times 15$ d), the severity of renal functional damage was greater in group B than in group C (Tab 1). SDS-PAGE showed that at month 0 the percentage of low molecular weight protein (MW < 20000) of urine in rats of group A (50 $g \cdot kg^{-1} \cdot d^{-1} \times 7$ d) was significantly higher than that of normal control group (48.08 % ± 5.19 % *vs* 24.99 % ± 1.94 %, $n = 4$, $P < 0.01$).

At month 1, all the renal functional parameter levels in the three dosage groups were shown to be approaching normal values. Only serum urea and creatinine levels in the highest dosage group (group A) were statistically significant ($P < 0.05$) compared to the normal control group (Tab 1).

At months 3 and 6, the renal function of rats in the three dosage groups was nearly normal, statistically not significant compared to the normal control group (Tab 1).

Histology

Month 0: In group A, histopathological changes, which were similar among 6 rats, showed acute tubular necrosis. Focal or patchy brush borders or cytoplasm of tubular epithelial cells were seen lost, predominantly at the corticomedullary junction (Fig 1). Basement membranes of tubules usually remained intact. Partial tubular lumens contained protein casts and ruptured cytoplasm. Focal brush borders or cytoplasm of tubular epithelial cells were seen lost in the proximal convoluted tubules of cortex. Congestion was observed in the peritubular capillaries. Edema, widening, and inflammatory cell infiltration were not observed in the interstitium. Mesangial matrix of glomeruli proliferated slightly. Blood vessel smooth muscles showed vacuolization. In group B and C, histopathological changes were similar to group A and the severity of renal injuries was less than group A.

Month 1: In group A, histopathological changes, which were similar among 6 rats, showed that the tubular lesions gradually recovered. Focal brush borders or cytoplasm of tubular epithelial cells were seen lost at the corticomedullary junction (Fig 2A). Small focal interstitial infiltration of inflammatory cells was observed (Fig

Tab 1. Effect of *Aristolochia manshuriensis* Kom on renal function of rats. $n = 6$ rats. $\bar{x} \pm s$. Compared to the same month: $^{b}P < 0.05$, $^{c}P < 0.01$ *vs* D. $^{e}P < 0.05$, $^{f}P < 0.01$ *vs* C. $^{h}P < 0.05$, $^{i}P < 0.01$ *vs* B.

Dosage/ $g \cdot kg^{-1} \cdot d^{-1} \times d$	Serum urea/ $mmol \cdot L^{-1}$	Serum creatinine/ $\mu mol \cdot L^{-1}$	Urinary NAG/ $U \cdot g^{-1}$ (creatinine)	24-h urinary protein/mg	24-h urinary glucose/μmol	Urinary volume/mL	Urinary osmolality/ $mOsm \cdot L^{-1}$
Month 0							
A (50×7)	29.4 ± 7.6^{cfi}	170.7 ± 43.9^{cfi}	209 ± 188^{cfi}	60 ± 37^{c}	282 ± 207^{cfi}	17 ± 11^{c}	729 ± 78^{cf}
B (30×7)	14.4 ± 3.6^{b}	78.0 ± 5.8^{a}	44 ± 10^{c}	46 ± 11^{ce}	40 ± 19^{ce}	14 ± 5^{b}	808 ± 80^{cf}
C (20×15)	11.7 ± 1.9^{b}	75.2 ± 5.3	41 ± 9^{b}	27 ± 7^{c}	17.4 ± 1.7^{b}	10.5 ± 2.0^{b}	1123 ± 153
D (normal control)	7.1 ± 0.9	69.7 ± 3.2	22 ± 7	8 ± 3	14.9 ± 1.2	6.4 ± 2.2	1558 ± 385
Month 1							
A (50×7)	9.2 ± 1.4^{b}	73.0 ± 3^{b}	20 ± 5	17 ± 9	18.4 ± 3.8	6.0 ± 1.7	1267 ± 142
B (30×7)	8.4 ± 1.2	71.7 ± 4.5	23 ± 12	11 ± 6	16.6 ± 1.9	6.0 ± 2.1	1370 ± 171
C (20×15)	7.8 ± 0.5	70.3 ± 5.4	23 ± 12	10 ± 3	15.5 ± 1.4	6.3 ± 1.2	1497 ± 277
D (normal control)	7.0 ± 0.7	66.3 ± 4.7	24 ± 6	8.6 ± 1.8	15.4 ± 2.0	7.7 ± 3.6	1523 ± 248
Month 3							
A (50×7)	7.8 ± 1.6	76.3 ± 2.8	28 ± 6	12.8 ± 1.6	16.8 ± 1.3	7.1 ± 3.0	1410 ± 369
B (30×7)	7.6 ± 1.2	70.3 ± 4.3	29 ± 11	10 ± 6	16.0 ± 1.5	6.2 ± 2.7	1547 ± 195
C (20×15)	7.80 ± 0.21	72.0 ± 3.9	24 ± 7	9 ± 4	16.6 ± 1.6	6.9 ± 3.9	1590 ± 205
D (normal control)	7.6 ± 0.5	71.0 ± 4.7	27 ± 9	10 ± 5	16.2 ± 2.2	7.7 ± 3.8	1557 ± 94
Month 6							
A (50×7)	8.0 ± 1.4	71.0 ± 3.2	21 ± 11	15.1 ± 6.8	20.2 ± 3.5	10.4 ± 4.4	1426 ± 230
B (30×7)	7.9 ± 0.7	71.3 ± 4.5	26 ± 13	13.4 ± 4.8	16.9 ± 3.4	6.8 ± 3.2	1400 ± 190
C (20×15)	7.3 ± 0.5	69.3 ± 2.5	20 ± 14	8.0 ± 2.4	11.2 ± 0.5	7.5 ± 2.5	1320 ± 505
D (normal control)	7.5 ± 0.6	65.2 ± 6.5	29 ± 11	9.1 ± 4.3	15.5 ± 3.8	6.9 ± 1.6	1592 ± 416

2B). Basophilic deposits were occasionally observed in the tubular epithelial cytoplasm in HE sections (Fig 2C). In von Kossa's stain, the basophilic deposits stained yellow-brown (Fig 2D) instead of black, which suggested that the substances were not calcium deposits. Mesangial matrix of glomeruli proliferated slightly. Blood vessel smooth muscle showed vacuolization. In group B and C, histopathological changes, which were similar to group A, showed that the tubular lesions gradually recovered. Small focal interstitial infiltration of inflammatory cells was also observed. Basophilic deposits were not found.

Month 3: In group A, histopathological changes, which were similar among 6 rats, showed nearly restored tubular lesions (Fig 3A). Few scattered tubular epithelial cells were seen lost at the corticomedullary junction. Basophilic deposits were not observed. Multifocal interstitial infiltration of inflammatory cells was observed (Fig 3B). Abnormal mitosis and nuclear anaplasia were not found. Mesangial matrix of glomeruli proliferated slightly. Blood vessel smooth muscle showed vacuolization. In group B and C, histopathological changes were similar to group A.

Month 6: Histopathological changes, which were similar among the three dosage groups, showed that the tubular lesions nearly recovered. Few scattered tubular epithelial cells were seen lost at the corticomedullary junction. Interstitial infiltration of inflammatory cells was not prominent. And basophilic deposits were not found. Renal preneoplastic lesions, renal tumors, and extrarenal tumors were observed in rats.

At month 6, the occurrence of renal preneoplastic lesions at dosages of 50 $g \cdot kg^{-1} \cdot d^{-1}$, 30 $g \cdot kg^{-1} \cdot d^{-1}$, and 20 $g \cdot kg^{-1} \cdot d^{-1}$ was 100.0 % for each dose. In preneoplastic lesion area, the short spindle-shaped interstitial cells, which surrounded the remnant atrophic tubules, were in patches or arranged diffusely, with cytoplasm thinly stained and nuclear hyperchromasia (Fig 4A). Abnormal mitoses were easily observed. Edema could be observed in partial interstitium. Tubular dilation was occasionally seen, and huge protein casts could be found.

At month 6, the occurrence of renal tumors at dosages of 50 $g \cdot kg^{-1} \cdot d^{-1}$, 30 $g \cdot kg^{-1} \cdot d^{-1}$, and 20 $g \cdot kg^{-1} \cdot d^{-1}$ was 42.8 %, 25.0 %, and 0 %, respectively, including 4 cases of renal mesenchymal tumor and 1

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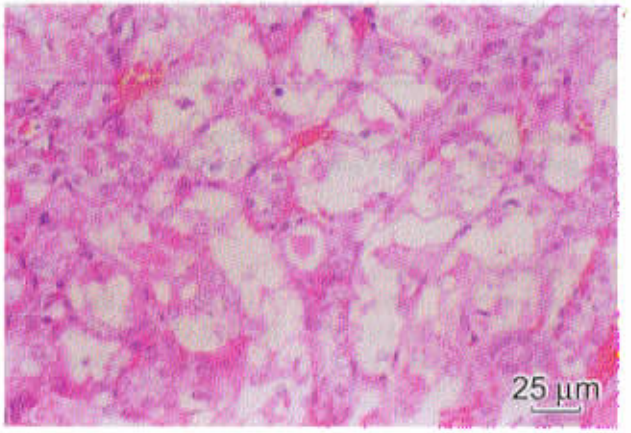

Fig 1. At month 0, renal histopathological changes showed acute tubular necrosis. Patchy brush borders or cytoplasm of tubular epithelial cells were seen lost, predominantly at the corticomedullary junction (HE × 400).

case of nephroblastoma. Microscopically, renal mesenchymal tumors consisted of short spindle-shaped tumor cells which were diffused arranged, with cytoplasm red stained or thinly stained and nuclear hyperchromasia (Fig 4B). Abnormal mitoses and nuclear anaplasia were easily observed. Microscopically, nephroblastoma consisted of two kinds of histological compositions: epithelial and stroma elements.

At month 6, the occurrence of extrarenal tumors was 14.4 %, 12.5 %, and 12.5 % respectively, including tumor of ductal epithelium of the breast, tumor of follicular epithelium of the thyroid and tumor of appendage epithelium of the skin.

The occurrence of renal preneoplastic lesions, renal tumors, and extrarenal tumors in normal control group was 0 %.

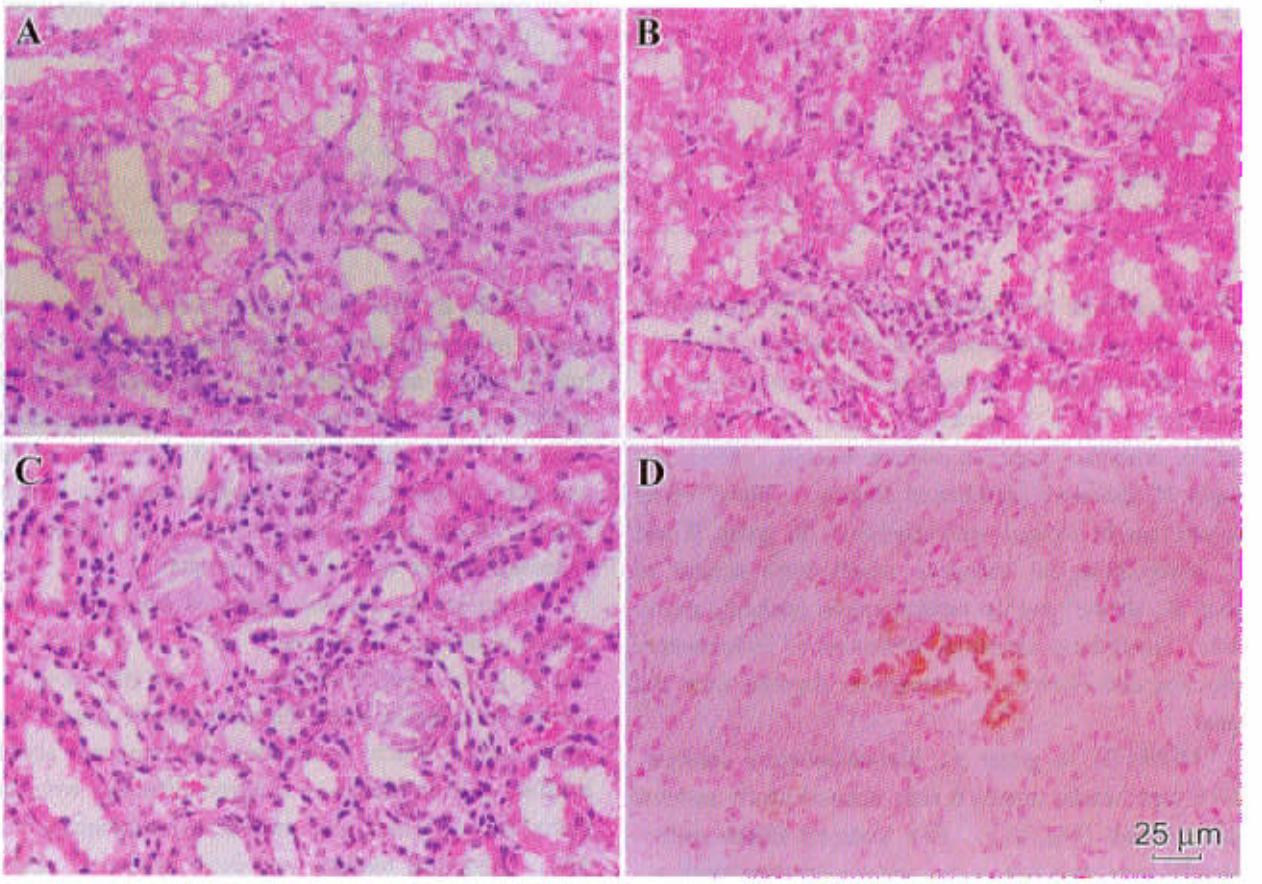

Fig 2. Renal histopathological changes at month 1. (A) Acute tubular necrosis in recovery stage. Focal brush borders or cytoplasm of tubular epithelial cells were seen lost at the corticomedullary junction (HE × 400). (B) Small focal interstitial infiltration of inflammatory cells could be seen (HE × 400). (C) Basophilic deposits were occasionally observed in the tubular epithelial cytoplasm (HE × 400). (D) In von Kossa's stain, the basophilic deposits were stained yellow-brown instead of black, which suggested that the substances were not calcium deposits (von Kossa × 400).

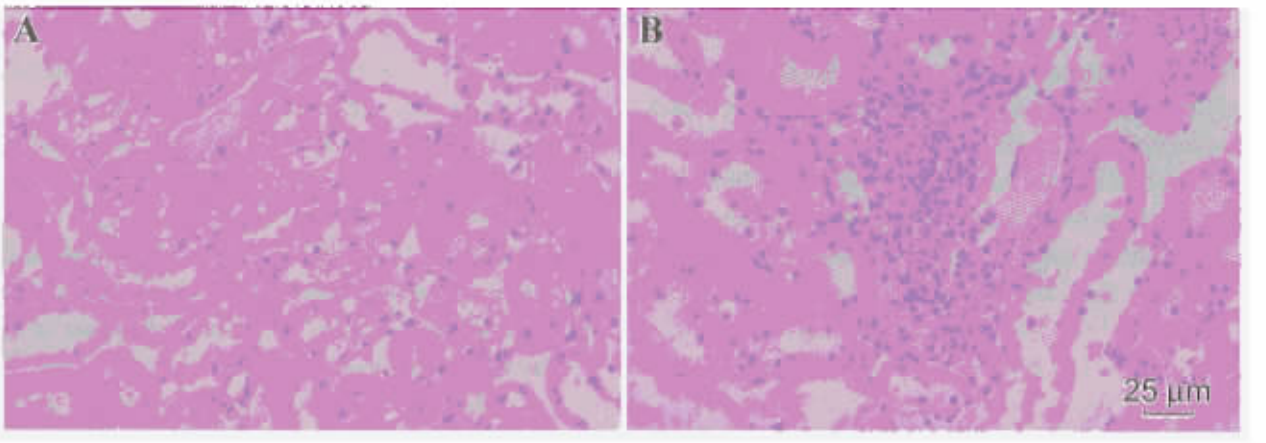

Fig 3. Renal histopathological changes at month 3. (A) The tubular lesions at the corticomedullary junction were nearly restored (HE × 400). (B) Mutifocal interstitial infiltration of inflammatory cells could be seen (HE × 400).

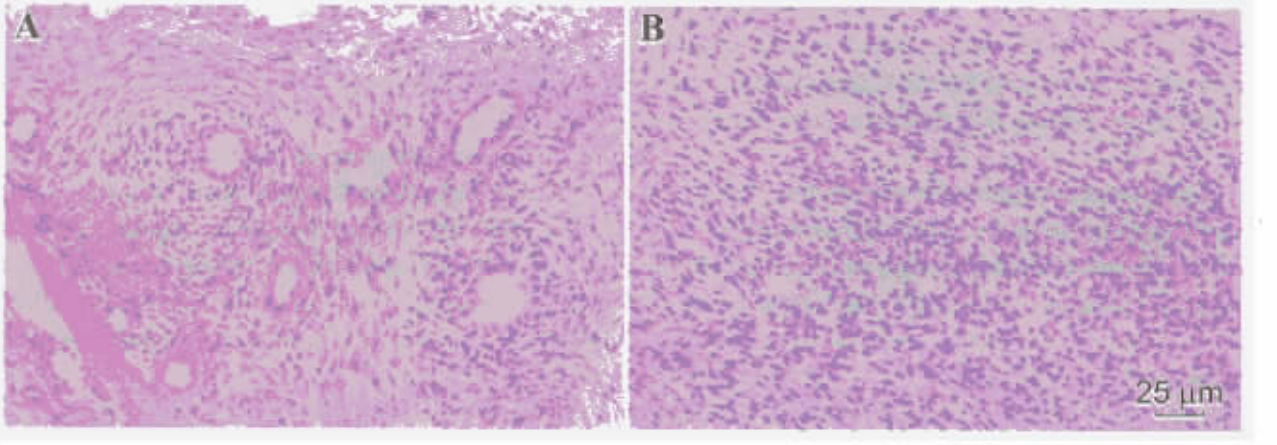

Fig 4. Renal histopathological changes at month 6. (A) Renal preneoplastic lesions. The short spindle-shaped interstitial cells, which surrounded the remnant atrophic tubules, were diffusely arranged, with cytoplasm thinly stained and nuclear hyperchromasia (HE × 400). (B) Renal mesenchymal tumors. The short spindle-shaped tumor cells were diffusely arranged, with cytoplasm red stained or thinly stained and nuclear hyperchromasia (HE × 400).

DISCUSSION

Functional and histopathologic changes of acute renal injury induced by *Aristolochia manshuriensis* Kom The renal functional changes of acute renal injury induced by *Aristolochia manshuriensis* Kom included azotemia, low molecular weight proteinuria, glycouria, urinary hypoosmolality, and NAG enzymuria. Histopathological changes showed acute tubular necrosis, with brush borders or cytoplasm of tubular epithelial cells lost, predominantly at the corticomedullary junction, which is most sensitive to ischemia and anoxia, induced by nephrotoxin. Ischemia and anoxia, influencing each other, aggravated the lesions in this region. Tubules involved included proximal convoluted tubules, distal convoluted tubules, Henle's loops, and collecting ducts. The injury of proximal convoluted tubules led to the dysfunction of reabsorption, followed by renal glycoguria and low molecular weight proteinuria. The elevation of urinary NAG activity is an early marker of the destruction of the structural integrity of proximal tubular epithelium. The injury of distal convoluted tubules and Henle's loops led to the dysfunction of urine concentration, manifested by polyuria and urinary hypoosmolality. Functional and

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histopathologic changes of acute renal injury induced by *Aristolochia manshuriensis Kom* in rats are quite identical to those in patients intoxicated with the Chinese herb. Early pathological changes in renal biopsy mainly included acute tubular necrosis and edema of interstitium[1-3].

Nephrotoxicity of *Aristolochia manshuriensis* Kom in short-term large dosage pattern was more severe than in long-term small dosage pattern It is of interest that, although the cumulative dose of group B ($30\ g \cdot kg^{-1} \cdot d^{-1} \times 7\ d$) was apparently smaller than that of group C ($20\ g \cdot kg^{-1} \cdot d^{-1} \times 15\ d$), the renal function of the former was worse than that of the latter. The morphologic changes from month 0 to month 3 followed the same trend. At month 6, the occurrence of renal tumor or systemic tumor of group B ($30\ g \cdot kg^{-1} \cdot d^{-1} \times 7$ d) was apparently higher than that of group C ($20\ g \cdot kg^{-1} \cdot d^{-1} \times 15$ d). This suggested that the nephrotoxicity of *Aristolochia manshuriensis* Kom in short-term large dosage pattern was more severe than that in a long-term small dosage pattern, which is also supported by the clinical observation that the Chinese herb is usually ingested by the patients in a short-term large dosage pattern.

Long-term morphologic observation of acute renal injury induced by *Aristolochia manshuriensis* Kom in rats showed no sign of chronic tubulo-interstitial lesions At month 1, the tubular lesions of rats in group A, B, and C partially recovered. At months 3 and 6, the tubular lesions of rats in group A, B, and C were observed to be nearly restored. The morphologic observation showed no sign of chronic tubulo-interstitial lesions. This is different from the morphologic changes observed in patients intoxicated with the Chinese herb[2-3], and is also different from morphologic changes observed in patients with Chinese Herb Nephropathy[10-13]. Whether this difference is due to the species of animals remains to be further investigated.

The patients intoxicated with *Aristolochia manshuriensis* Kom usually followed a chronic course, with persistent increase in serum creatinine level. Pathological findings in renal biopsy showed that tubular lesions exist persistently. At last the patients develop chronic interstitial nephritis, with interstitial widening and fibrosis, or even go into end stage renal failure[13]. It is assumed that the patients intoxicated with the Chinese herb have already suffered from kidney diseases and the nephrotoxicity of the Chinese herb triggers a renal fibrotic process that progressively destroys the kidney. The possibility remains to be elucidated further.

Long-term morphorlogic observation of acute renal injury induced by *Aristolochia manshuriensis* Kom in rats showed that interstitial infiltration of inflammatory cells was not prominent At months 1 and 3, only a few inflammatory cells were observed infiltrating in the interstitium, which was similar to pathological findings of renal biopsy.

In interstitial nephritis caused by drugs, tubular degeneration and atrophy, and interstitial edema and fibrosis, generally accompanied by cellular infiltration of single nuclear or eosinophils, are commonly found[14]. Such morphologic changes were not found in this study.

Basophilic deposits were observed in the tubular epithelial cytoplasm in HE sections In von Kossa's stain, the basophilic deposits observed in HE sections stained yellow-brown instead of black, which suggested that the substances were not calcium deposits. Whether the basophilic deposits existed or not depended upon the experimental dosage and time. At month 0, the substances were not observed. At month 1, the basophilic deposits were only observed in group A, the occurrence was low (16.7 %). At months 3 and 6, the substances were not observed. In the patients intoxicated with *Aristolochia manshuriensis* Kom, it could also be found that the similar basophilic deposits protruded through epithelial layers into the tubular lumina. In electron microscopy, these materials exhibited layer-like structures. Even after 6 months, on renal rebiopsy these materials still existed[3].

The chemical properties of these materials remain to be further investigated. It is supposed that the materials were the metabolic products of cells[1]. When the structure and function of tubular epithelial cells are normal, the elimination of these materials can be performed by organic anions or organic cations transport systems. When tubular epithelial cells are injured, these materials may deposit in the tubular epithelial cells. With the degeneration and necrosis of tubular epithelial cells, these materials may enter into the lumina.

***Aristolochia manshuriensis* Kom was proved to be oncogenic** At month 6, renal tumors and extrarenal tumors occurred in rats, and exhibited a dose-dependent pattern. The renal tumors were microscopically diagnosed as renal mesenchymal tumors and nephroblastoma, which suggested that tumors were probably derived from primitive undifferentiated cells, which could differentiate into both epithelial tissues and mesothelial tissues. Extrarenal tumors included tumor of ductal epithelium of the breast, tumor of follicular epithelium of the thyroid,

and tumor of appendage epithelium of the skin, which were all epithelium originated. The pathology and immunohistochemistry of these tumors are being further investigated. At present, it has not been reported that the patients intoxicated with *Aristolochia manshuriensis* Kom may develop tumors. However, the carcinogenicity of *Aristolochia manshuriensis* Kom is a serious problem to be dealt with.

In summary, 1) Administration of large dosage of *Aristolochia manshuriensis* Kom can induce acute renal failure in rats. 2) The long-term renal function and histopathologic changes of acute renal injury induced by *Aristolochia manshuriensis* Kom recovered spontaneously. 3) *Aristolochia manshuriensis* Kom was proved to be oncogenic for the first time.

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木通所致大鼠急性肾损伤的远期效应

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关键词 木通; 肾毒性; 急性肾功能衰竭; 间质性肾炎; 肾病; 肿瘤

目的: 观察木通所致大鼠急性肾损伤的远期效应(功能及组织形态学改变特点). **方法**: 用不同剂量木通水煎剂(50 g·kg^{-1}·d^{-1}×7 d、30 g·kg^{-1}·d^{-1}×7 d、20 g·kg^{-1}·d^{-1}×15 d)给大鼠灌胃, 建立大鼠急性肾损伤动物模型后, 检测实验开始(给药结束之日)、1月、3月、6月时各种肾功能指标, 及肾组织形态学的变化. **结果**: 1) 木通所致大鼠急性肾损伤的近期功能改变为, 氮质血症、低渗尿、低分子蛋白尿、糖尿、尿NAG酶升高. 组织形态学改变主要为急性肾小管坏死, 以皮髓交界区小管损伤为主. 2) 实验1月、3月木通组大鼠的肾功能逐渐恢复, 皮髓交界区小管病变逐渐恢复, 小管上皮细胞胞浆内可见嗜碱性物质沉积, 间质浸润细胞较少, 未见间质慢性炎症和纤维化等慢性化病变. 3) 实验6月大鼠发生肾脏间质肿瘤样增生及全身性肿瘤. **结论**: 1) 大剂量木通可导致大鼠急性肾功能衰竭. 2) 木通所致大鼠急性肾损伤远期其肾功能及小管损伤可逐渐恢复, 未见明显小管间质慢性化病变. 3) 木通具有致肿瘤作用.