DNA ADDUCTS FORMED BY ARISTOLOCHIC ACID IN RENAL TISSUE

<table>
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<tr>
<th>Chinese Herb Nephropathy (n = 5)</th>
<th>Controls (n = 6)</th>
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<td>0.7–5.3 per 10⁷ nucleotides</td>
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CLINICAL FEATURES OF CHINESE HERB NEPHROPATHY

Rapidly progressive renal failure
- Microproteinuria of tubular type
- Unremarkable urinary sediment
- Small and shrunken kidneys
- Valvular heart diseases (dexfenfluramine-associated therapy), 30%
- Associated urothelial cancers

FIGURE 10-39

The clinical features of Chinese herbs nephropathy are characterized by rapidly progressive renal failure without both urinary sediment abnormalities and proteinuria except for a microproteinuria of tubular type. The kidneys are small and shrunken. Vascular heart diseases are associated in 30% of cases (probably owing to dexfenfluramine administered with the Chinese herbs for slimming purposes) [35]. Some cases of associated urothelial cancers also are described [36,37].

FIGURE 10-38

DNA aristolochic acid adducts in kidney tissues of patients with Chinese herbs nephropathy. The role of Aristolochia in the pathogenesis of Chinese herbs nephropathy was confirmed by the demonstration of DNA aristolochic acid adducts (a biomarker of aristolochic acids exposure) in renal tissue of patients with Chinese herbs nephropathy, whereas these adducts were absent in the renal tissue of control cases. (Adapted from Schmeiser and coworkers [34].)

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FIGURE 10-40

Photographic image of the pathology of Chinese herbs nephropathy. Chinese herbs nephropathy is characterized by a large reduction in kidney volume. Moreover, an associated tumor of the lower ureter is shown.

FIGURE 10-41 (see Color Plate)

Pathology of Chinese herb nephropathy. The major pathologic lesion consists of extensive interstitial fibrosis with atrophy and loss of the tubules, predominantly located in superficial cortex [38,39]. A, A low-power view of transition between superficial cortex (left) and deep cortex (right) shows an extensive interstitial fibrosis with relative sparing of glomeruli. (Masson trichrome stain, magnification × 50.) B, A normal glomerulus surrounded by a paucicellular interstitial fibrosis and atrophic tubules. (Masson's trichrome stain, magnification × 300.)
Proximal tubular injury in Chinese herbs nephropathy is demonstrated by a significant increase in urinary excretion of microproteins (Clara cell protein, CC16; β2-microglobulin [β2-m] and retinol binding protein [RBP]) as well as a decrease in urinary excretion of neutral endopeptidase (NEP) a marker of the brush border tubular mass. (Adapted from Nortier and coworkers [40].)

Chinese herbs nephropathy and renal pelvic carcinoma. Urothelial cancers are associated with Chinese herbs nephropathy [36,37]. Shown is a filling defect (arrow) in the renal pelvis in an antegrade pyelogram obtained from a patient with Chinese herbs nephropathy and hematuria. (From Vanherweghem and coworkers [37]; with permission.)
Pathology of urothelial tumors associated with Chinese herbs nephropathy. Microscopic pattern is shown of a lower urothelial tumor obtained by ureteronephrectomy of a native kidney in a patients with transplantation who has Chinese herbs nephropathy (the macroscopic appearance of the nephrectomy is shown in Fig. 10-40). A, Part of the urothelial proliferation. Plurifocal thickening of the urothelium is present. (Hematoxylin and eosin stain x 50.) B, In situ transitional cell carcinoma with high mitotic rate. (Magnification x 400 periodic acid-Schiff reaction.)

FIGURE 10-45
Effects of steroids on the evolution of renal failure in Chinese herbs nephropathy. Steroid therapy was shown to decrease the evolution of renal failure in a subgroup of patients with Chinese herbs nephropathy [41]. The evolution is shown of the 1/P creatinine ratio of patients with Chinese herbs nephropathy, 12 of whom were treated with steroids as compared with 23 not treated with steroids (control group). In the control group the 1/P creatinine curve was limited to 6 months of follow-up because at 12 months, 17 of the 23 patients were on renal replacement therapy. (From Vanherweghem and coworkers [41]; with permission.)

TOXIC CHRONIC INTERSTITIAL NEPHROPATHIES WITH UROTHELIAL CANCERS

Analgesic nephropathy (phenetidin compounds)
Balkan nephropathy (ochratoxins)
Chinese herbs nephropathy (aristolochic acids)

FIGURE 10-46
Of interest is the association between chronic renal interstitial fibrosis and urothelial cancers. This association appears, at least, in three chronic toxic nephropathies: analgesic nephropathy, Balkan nephropathy, and Chinese herbs nephropathy. This association indicates that nephrotoxins promoting interstitial fibrosis (analgesics, ochratoxins, and aristolochic acids) also may be oncogenic substances.
References


