A 75-year-old Chinese male was admitted to hospital with a 1 week history of ankle oedema, facial puffiness and frothy urine. He had no sore throat, smoky urine, rash, joint pain, fever, night sweat or weight loss. He did not experience shortness of breath. Five weeks before, he was admitted for insidious onset of right-sided weakness with a 1 year history of chronic neck pain after an accidental fall. He was then found to have prostate enlargement with a hard nodule. He had no family history of renal disease. He did not smoke or drink. His blood pressure measured 180/100 mmHg. Clinically, he had ankle oedema and had no lymphadenopathy. Jugular venous pressure was not elevated. His abdomen was soft and non-tender. No organomegaly was found. He had a right pyramidal weakness (power grade: 4 over 5) and hyperreflexia over right-sided limbs. Initial investigation showed features of nephrotic syndrome and advanced renal impairment (spot urine: no microscopic haematuria; 24 h urine protein: 7.74 g/day; creatinine on admission: 341 μmol/l; serum albumin: 23 g/dl; hypercholesterolaemia: 9 mmol/l; adjusted calcium: 2.99 mmol/l; urate: 0.33 mmol/l). Rheumatoid factor was 24 IU (normal: <20 IU). Anti-nuclear factor, anti-neutrophil cytoplasmic antibody and HBsAg were all negative. Complement levels and immunoglobulin pattern were normal. Renal ultrasonogram showed normal-sized kidneys with chronic parenchymal change. Prostatic-specific antigen was raised. Contrast computerized-tomography brain scan and a later magnetic resonance imaging scan of the brain and neck showed cerebral infarction and no evidence of cerebral tumour or cervical spinal cord compression. At that juncture, a diagnosis of nephrotic syndrome complicated by cerebral thrombosis due to hypercoagulability was made. Renal biopsy was performed. He was asked to limit his fluid intake to <1 l/day. His oedema responded to intermittent doses of intravenous frusemide. With a gradual weight loss of 10 kg during admission, his creatinine decreased gradually from 341 to 136 μmol/l before hospital discharge. His creatinine was 124 μmol/l at 1 week after discharge. His acute renal deterioration was believed to be related to the novel mechanism of tubular oedema and obstruction secondary to the oedematous state of his nephrotic syndrome. While the oedema subsided with diuretics, serum creatinine level improved. He was planned to be followed-up in 3 weeks with a definite treatment plan. Two weeks after discharge, however, he was readmitted following one week of repeated vomiting, anorexia and decreased urine output. No fever, loin pain, haematuria or muscle ache was noted. Clinically, he had ankle oedema, raised jugular venous pressure and bilateral basal lung crepitations.

Advanced renal impairment (sodium 142 mmol/l, potassium 5.3 mmol/l, urea 41 mmol/l, creatinine 1936 μmol/l), severe metabolic acidosis (pH 7.2, pCO₂ 2.24 KPa, pO₂ 19 KPa, HCO₃ 6.6 mmol/l), hypocalcaemia (1.27 mmol/l) and hyperphosphataemia (3.68 mmol/l) were found. His earlier renal biopsy (Figure 1) performed during the previous admission revealed a case of focal segmental glomerulosclerosis (FSGS) with patchy tubular atrophy and chronic inflammatory infiltrate. In view of the uncertain cause of acute renal failure complicating FSGS, another renal biopsy was performed after three sessions of haemodialysis. Interstitial nephritis with significant interstitial fibrosis and some element of acute tubular necrosis (Figure 2) was found in the second renal biopsy. Further detailed inquiry revealed a 10 day history of daily ingestion of a Chinese herbal medicine as a ‘tonic herbal remedy’ for the patient’s stroke 2 weeks before the present admission. The blood and herbs mixture as well as the written herbal prescription were submitted to a local toxicology
centre and later a specialized laboratory for identification and assay of herbal nephrotoxins. Two potential nephrotoxic herbs, mutong (*Aristolochia manshurien-sis*) and fangchi (*A. fangchi*), were identified from both the written herbal prescriptions and herbs mixtures. Aristolochic acid types I and II were found by high performance liquid chromatography–diode array detection (HPLC–DAD) in fangchi, one of the components of the herbal mixture. A diagnosis of aristolochic acid nephropathy (AAN) complicating FSGS was made. The patient was given prednisolone at a dose of 1 mg/kg/day. Renal function finally recovered and haemodialysis was terminated 4 weeks after the diagnosis of acute renal failure. His creatinine was stabilized at 187 μmol/l at 1 week after termination of haemodialysis. Prednisolone was then tailed down slowly at a rate of 5–10 mg per month. Unfortunately his course was complicated by severe pneumonia, 1 month after termination of haemodialysis. The patient finally succumbed.

In summary, this gentleman had fangchi-associated AAN complicating his underlying FSGS, presenting with acute renal failure requiring temporary haemodialysis for 4 weeks. Significant renal recovery resulted from treatment with systemic steroid.

**Discussion**

The diagnosis of AAN was based on a renal biopsy of interstitial nephritis and a history of herb ingestion. The latter was heavily hinted by the herbal prescription, which contained the known nephrotoxic herbs, fangchi and mutong. Subsequent identification of the nephrotoxic herbal sample was arranged with a specialized centre, which identified aristolochic acid types I and II in fangchi. The routine screening for prescribed drugs in the preparation submitted for analysis was negative. We did not confirm DNA adduct in the renal biopsy, which is a good tool to infer the presence of aristolochic acid in the body, as it can be demonstrated many years after ingestion of aristolochic acid-containing herbs. We believe the present case was a case of AAN as there was adequate circumstantial evidence to support the diagnosis with a known nephrotoxin, i.e. aristolochic acid. The degree of lymphocytic infiltration was more intense than in a usual case of chronic AAN. This would be due to renal biopsy early after ingestion of aristolochic acid (10 days after ingestion) in the present case, as found in a salt-depleted rat model [1]. Mutong is produced in several regions of China and not all kinds of mutong contain aristolochic acid. It is a common practice in Chinese medicine that the source of the herbs, and therefore the active ingredients, may change from time to time [2]. The presence of aristolochic should be confirmed by laboratory tests for all suspected herbal nephrotoxic agents. Identification of aristolochic acid can be done by HPLC–DAD in specialized laboratories [3]. A previous report suggested an average dose of 192.2 ± 13.1 g aristolochic acid-containing herbs was required to cause end-stage renal failure [4]. Despite the highly variable content of aristolochic acid in herbal powder [5], the dose of 100 mg *A. fangchi* (or 10 mg/day for 10 days) that was taken to produce end-stage renal failure in the present case is considered a smaller dose than that quoted previously. Increased susceptibility to AAN toxicity in glomerulonephritis and/or chronic renal disease (baseline creatinine clearance of 52 ml/min in the present case) remains a genuine possibility. Further studies involving patients with chronic renal disease and/or glomerulonephritis are required to confirm this point.

Eighteen days after ingestion of herbs, oral prednisolone was started and maintained for 4 weeks at a dose of 1 mg/kg/day, which resulted in a remarkable recovery of renal function. Although some degree of
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The recovery was thought to be due to recovery of acute tubular necrosis, the major component of the recovery was believed to be the result of treatment of interstitial nephritis related to AAN. A previous report suggested that AAN was at least partly due to an immunological mechanism [6], as the renal deterioration progressed in 58–75% of cases even when the incriminating herb was withdrawn [7,8]. Steroid treatment was found to be beneficial for AAN in a trial comparing it with historic control [6]. Further follow-up of the patients (n = 14) had found that steroids delay end-stage renal disease by 1–3 years when compared with control treatments [9]. Steroids were also useful in another series where patients either presented as Fanconi syndrome or as acute renal failure with features of acute tubular necrosis in renal biopsy [10]. However, in view of the potential side effects of steroids, as demonstrated in the present case as severe pneumonia, the lowest possible dose and duration of steroid requires further studies.

Aristolochic acid is a known carcinogen causing cancer of uroepithelial origin in the urinary tract due to the formation of DNA adduct in the uroepithelium [11]. Prostate cancer with an elevation of prostatic-specific antigen has not been reported with aristolochic acid. The temporal relationship also did not suggest aristolochic acid as a causative agent of carcinoma of prostate in this case.

To our knowledge, the present case is the first reported case of FSGS complicated by AAN with acute renal failure. A previous case series in Beijing reported three categories of AAN, namely those with acute renal failure associated with acute tubular necrosis (7%), Fanconi syndrome (12%) and chronic progressive AAN (81%) [10]. Physicians should be aware of AAN as an emerging cause of renal failure and renal progression in glomerular disease. Whether there exists a propensity of FSGS or other glomerulonephritis to be affected by aristolochic acid is unknown and requires further investigation.

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