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Asymptomatic renal failure in a patient with bipolar disease without lithium therapy

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A 48-year-old Chinese woman with a history of major depression and bipolar disease, controlled by bromazepam, clozapine, fluoxepine and lamotrigine for several years, presented with microscopic haematuria (red blood cells: 10–25 per high power field on urinalysis) and acute renal failure (serum creatinine: 1.6 mg/dL with a baseline value 0.8 mg/dL) upon routine health exam. She was referred to our hospital for further work-up. She denied any previous ingestion of lithium. Neither analgesics nor anti-inflammatory agents were used by the patient in the recent past. Her body weight (BW) was 71 kg. She showed no signs of dehydration, oedema, dysuria, fever, flank pain, oliguria, urinary frequency or urgency, joint pain or skin rash.

On physical examination, her blood pressure was 130/70 mmHg. Her 24-h urine protein was 400 mg. Urinalysis revealed red blood cells 5–10/HPF, protein 1+ and no glycosuria. Her serum creatinine was 1.5 mg/dL, urea nitrogen 15 mg/dL and albumin 4.0 g/dL. Serological tests, including complement levels, serum and urine protein electrophoresis, C-reactive protein, rheumatoid factor, antinuclear antibody, anticardiolipin antibodies, immunoglobulins G, A and M, and markers for human immunodeficiency virus and hepatitis C and B, were all negative or within normal limits. A renal biopsy was performed (Figures 1,2,3,4).

What lesions are expected to be found in the renal biopsy?
What is the pathological diagnosis?
What is the clinical diagnosis?

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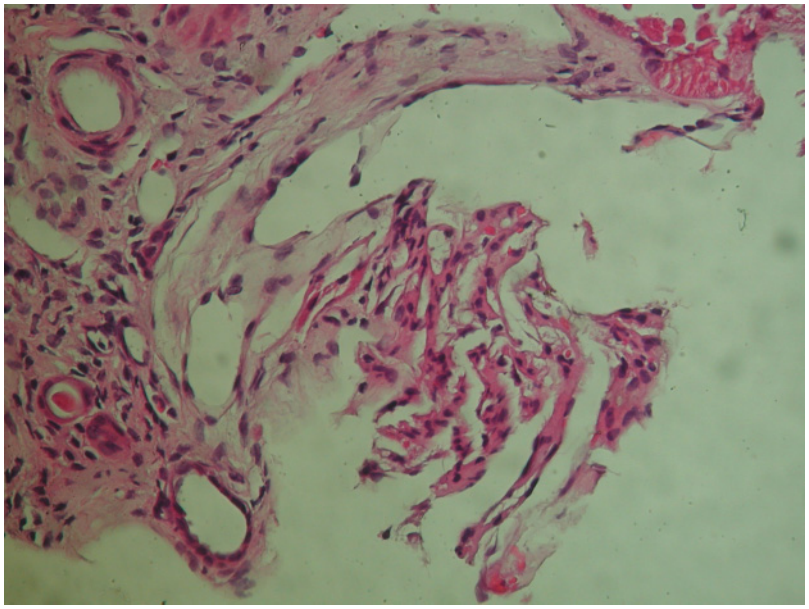

Fig. 1. Neither thickening of the basement membrane nor increase of the matrix and cellularity in the glomerulus is seen. The glomerulus is grossly normal (light microscopy, haematoxylin and eosin stain; original magnification ×400).

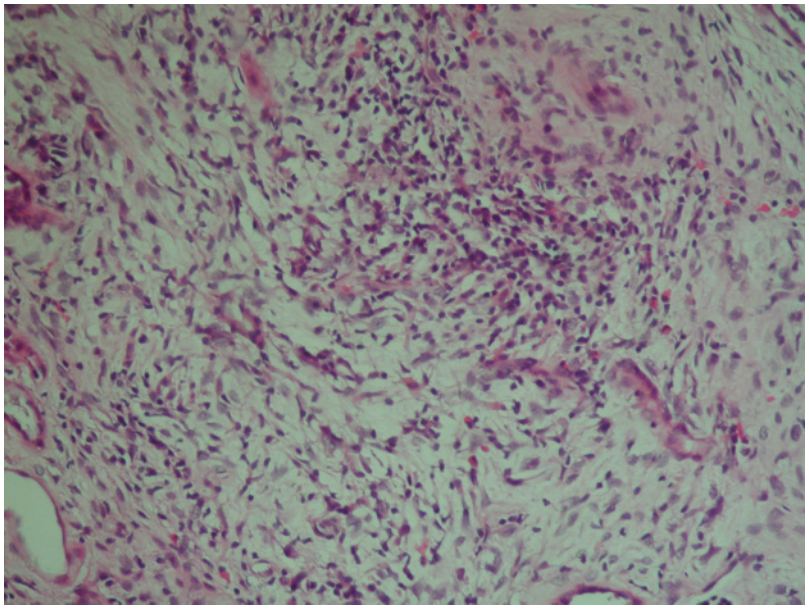

Fig. 2. Marked expansion with oedema and fibrosis is revealed in the interstitium. Infiltration and inflammation of lymphocyte and eosinophil are common. There appears atrophy of the renal tubules and sloughing of the tubular epithelium (light microscopy, haematoxylin and eosin stain; original magnification ×400).

The pathological diagnosis: both acute and chronic tubulo-interstitial nephritis with a suspected drug use causality

Biopsy showed no thickening of the basement membrane, no increase in matrix and a lack of hypercellularity in the glomeruli.

Gross features of glomeruli were normal (Figure 1). The interstitium showed a marked expansion with oedema and fibrosis. Inflammation and infiltration by lymphocytes and eosinophils were common. There was atrophy of the renal tubules and sloughing of the tubular epithelium (Figure 2). Apparent interstitial expansion and fibrosis were also evident upon masson-trichrome staining (Figure 3).

Direct immuno-fluorescence (DIF) showed strong fibrinogen deposits in the interstitium (Figure 4). There were no deposits of immunoglobulins A, M, G, C3 or C4. Pathological findings indicated that a drug-related tubulo-interstitial nephritis with both acute and chronic courses should be of first consideration. On further questioning, the patient reported having taken a Chinese herb medicine

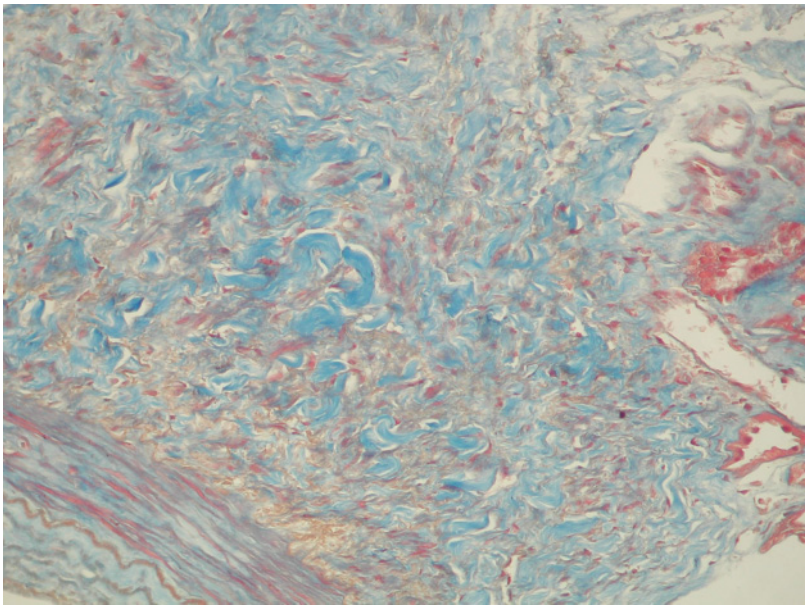

Fig. 3. Apparent interstitial expansion and fibrosis are also evident under masson-trichrome stain (light microscopy, masson-trichrome stains; original magnification ×400).

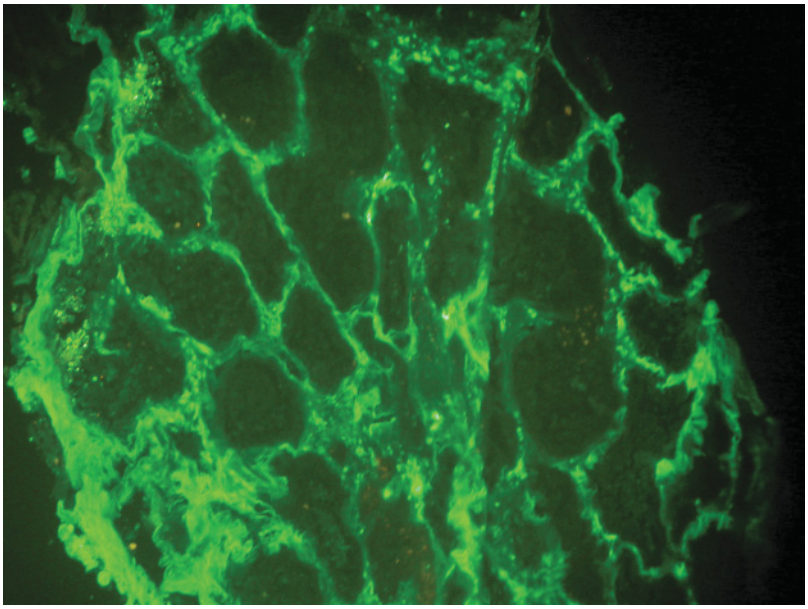

Fig. 4. Direct immuno-fluorescence (DIF) showed strong fibrinogen deposits in the interstitium. There were no deposits of immunoglobulins A, M, G, C3 and C4 (DIF, original magnification ×400).

(slimming regimen) for 3 months prior to the event in order to achieve weight loss.

She was instructed to halt the Chinese herb regimen. Following this, the microscopic haematuria disappeared after 1 week and serum creatinine level remained at 1.5 mg/dL thereafter.

The clinical diagnosis: Chinese herb nephropathy

The increasing popularity of Chinese herbal medicines has been illustrated by US national surveys showing 25% increases in the overall prevalence of use between 1990 and 1997. In 2003, European countries also spent almost 5 billion USD on over-the-counter Chinese herbal medicines. Reports from Japan, Taiwan and certain developing countries have indicated that herbal medicines used in locally compounded preparations receive equal status with US medical practices [1].

The clinical entity, initially called Chinese-herb nephropathy (CHN), was more accurately named aristolochic acid (extracts of herbal preparations) nephropathy (AAN) following dramatic cases in Belgium that illustrated the devastating consequences of inappropriate use of herbal

medicine [2]. In initial reports, AAN had been described as a pauci-symptomatic chronic renal failure (chronic AAN) with little proteinuria or urinary sediment. Severe anaemia was a predominant sign in some cases. Pathologically, an extensive interstitial pauci-cellular fibrosis was observed in the superficial cortex, mainly composed of proximal tubules with severe atrophy, and this progressed towards the deep cortex. The glomeruli remained intact at least in the beginning of the disease [3].

However, other clinical presentations, such as AAN, were described as early as 1992. Cases of renal failure rapidly progressing to end-stage renal disease (ESRD) were reported in Belgium, and these were associated with daily intake of slimming pills which included extracts from Chinese herbs [2,4,5]. Moreover, activated metabolites formed from nitro reduction of aristolochic acid (AA), called aristolactams, are able to form DNA adducts with adenosine and guanosine. These DNA adducts cause gene mutations that have been conclusively associated with urothelial malignancy [6].

The clinical course of AAN has been related to the intensity of AA exposure. For example, we found a positive correlation between the estimated total ingested dose of Aristolochia sp. and the severity of renal dysfunction [5]. Following the observation that inflammatory cells had infiltrated the interstitium in renal biopsy specimens, a pilot study showed that corticosteroids produced a slowing of renal failure progression in several patients, suggesting an immunological involvement in the still unknown mechanisms linking AA intoxication to renal fibrosis [4].

Despite strong warnings from the Food and Drug Administration (FDA) in 2001, many compounds containing AA are still currently sold worldwide. Herbal remedies should be submitted to quality controls and regulations as dangerous over-the-counter medicines, and these regulations should be as strict as for any conventional drug. Up to now, therapeutic strategies have been mainly conservative and included cessation of the offending agents after detection of renal insufficiency. When faced with renal disease or urothelial carcinoma of ‘unknown origin’, nephrologists and urologists should extend their clinical inquiry to the frequent use of ‘non-western’ medicine [1,6].

Conflicts of interest statement. None declared.

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