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BRIEF REPORT

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Fanconi's syndrome, interstitial fibrosis and renal failure by aristolochic acid in Chinese herbs

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Abstract Aristolochic acid-associated nephropathy (AAN) has been identified as a separate entity of progressive tubulo-interstitial nephropathy. Its characteristic pathological findings, including hypocellular interstitial fibrosis, intimal thickening of interlobular and afferent arterioles with glomeruli sparing or mild sclerosis, have been identified. Many cases of AAN in adults have been reported in Taiwan as well as throughout the world, but it has seldom been described in children. We report on a 10-year-old boy who presented with severe anemia, Fanconi's syndrome, and progressive renal failure. Renal biopsy revealed typical findings of AAN. Aristolochic acids I and II were identified from a Chinese herb mixture ingested by the boy. AAN was diagnosed after other etiologies had been excluded. The case demonstrates the hazards of Chinese herbs with regard to children's health in Taiwan and suggests that more attention should be paid to this issue.

Keywords Aristolochic acid-associated nephropathy · Aristolochic acid · Fanconi's syndrome · Interstitial nephropathy

Introduction

Aristolochic acid-associated nephropathy (AAN) has been known to be a progressive tubulo-interstitial nephropathy that is caused by aristolochic acid (AA), a component of at least six types of Chinese herbs including the *Aristolochia* species *Mu-tong*, *Boui*, and *Mokutsu*, etc. [1, 2]. It was first discovered in a weight-loss program in Belgium during 1992–1993. Since that time, the term "Chinese herb nephropathy" has been widely used to describe nephropathy caused by Chinese herbs. However, since *Aristolochia fanchi* was incorrectly used by Belgian practitioners, aristolochic acid-associated nephropathy (AAN) is a more proper descriptive term than Chinese herb nephropathy (CHN).

Many cases of AAN in adults have been reported throughout the world since 1992, but it has seldom been described in children. In this case report, we describe a 10-year-old Taiwanese boy who presented with severe anemia, Fanconi's syndrome, and progressive renal failure. AAN was diagnosed by characteristic pathological findings and the identification of aristolochic acids I and II in the Chinese herb mixture ingested by the boy. Unfortunately, on admission, the boy was in the condition of irreversible terminal renal failure, and he will need lifelong dialysis unless he receives a kidney transplant. This case focuses attention on the little-known issue of the hazards of Chinese herbs with regard to children's health.

Case report

A 10-year-old Taiwanese boy was initially referred to the department of pediatrics at the Veterans' General Hospital of Taichung in November 2000 for evaluation of his short stature. He had frequently suffered from the common cold during the previous 3 years. To improve his health, his parents had been giving him Chinese herb medicines from their own herb store since early childhood. He had received scheduled vaccinations and did not have any episodes of systemic disease. The initial examination revealed severe anemia [hemoglobin (Hb) 4.4 g/dl]. However, his parents refused admission for further examination and he was lost to follow-up at our hospital. Six months later, the boy was sent to a local hospital because of dyspnea, and severe anemia and renal failure were discovered. After emergency dialysis he was transferred to our hospital again for further

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examination. On admission, he had an ill-looking appearance with clear consciousness. We traced his height growth from the school nurse's record. It had been approximately 1 to 2 standard deviations (SDs) below average for his age 4 years before, and progressed to below 2 SDs after 1 year. On admission, his height was 118 cm, which is less than 3 SDs below average [3]. His weight was 22.4 kg, which is about 1 to 2 SDs below average. Blood pressure was 160/104 mmHg. Respiratory rate and pulse rate were within the normal range. Other physical examination findings were normal except for a pale conjunctiva and grade II systemic heart murmur over the left lower sternal border.

Laboratory study results were the following (normal values and SI units in parentheses): hemoglobin 2.7 g/dl (11.5–14.5 g/dl; 27 g/l), sodium 142 mEq/l (137–153 mEq/l; 142 mmol/l), potassium 4.5 mEq/l (3.5–5.3 mEq/l; 4.5 mmol/l), chloride 109 mEq/l (95–105 mEq/l; 109 mmol/l), calcium 10.0 mg/dl (9.0–10.6 mg/dl; 2.5 mmol/l), serum creatinine 15 mg/dl (0.7–1.4 mg/dl; 1,326 μmol/l), blood urea nitrogen (BUN) 168 mg/dl (5–25 mg/dl; 119.9 mmol/l), phosphate 1.9 mg/dl (2.5–4.5 mg/dl; 0.61 mmol/l), and magnesium 2.4 mg/dl (1.7–2.8 mg/dl; 0.99 mmol/l). Urinary protein was 690 mg/day with predominant tubular-type protein distribution on electrophoresis. Clearance of creatinine was 7.71 ml/min per 1.73 m^2. Urinary β2-microglobulin was above 18,000 ng/ml (660–2,740 ng/ml). Spot urine glucose was 0.2 g/dl. Filtration excretion of phosphate was 57% (normal <25%). There was generalized elevation of a number of amino acids in his urine. The diagnosis of Fanconi's syndrome was established based on the cardinal symptoms, including phosphaturia, glucosuria, and generalized amino aciduria. Renal ultrasonography showed bilateral small kidneys with increased echogenicity. Renal biopsy demonstrated advanced tubular loss, atrophy, and hypocellular interstitial fibrosis involving more than 80% of the renal parenchyma. Of 45 glomeruli, 14 showed sclerosis; non-sclerotic glomeruli showed normocellularity with marked wrinkling of capillary walls. The overall picture was end-stage chronic interstitial nephritis consistent with induction by Chinese herbs (Fig. 1).

The Chinese herb mixture provided by his parents were analyzed, and presence of aristolochic acids I and II was demonstrated by separation of the acids with high-performance liquid chromatography (HPLC) and comparison with the standard chromatogram. Aristolochic acid-associated nephropathy was diagnosed from the clinical picture, pathological findings, and evidence of aristolochic acid. The analyzed herbs provided by his parents were in a brown mixture, which should be decocted before being taken. Furthermore, these decocted herbs were given with undefined frequency and variable amount; some of them were even given raw. It was quite difficult to quantify the dosage of AA.

During hospitalization, we arranged intermittent hemodialysis for the patient three times per week. Erythropoietin and vitamins were supplied. The hematocrit returned to the normal range, and the condition of the boy was stabilized. Despite the immediate cessation of ingestion of the Chinese herb medicine, progression of renal failure remained relentless and lifelong dialysis will be required unless the patient undergoes renal transplantation.

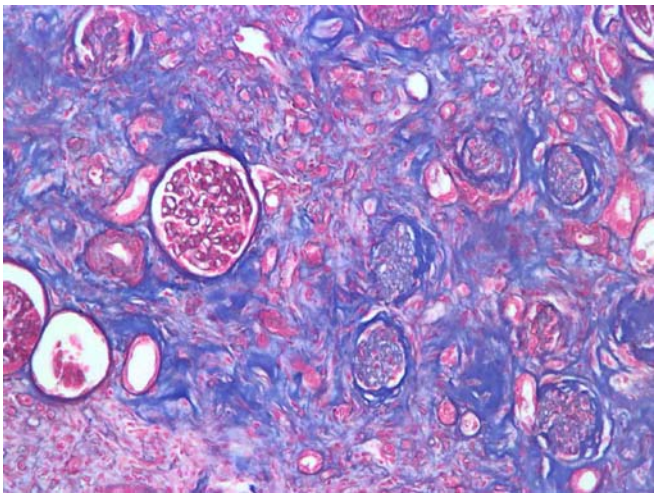

Fig. 1 Renal biopsy of the patient revealed advanced tubular loss, atrophy and interstitial fibrosis, involving more than 80% of the parenchyma. Inflammatory cell infiltration is minimal, which is characteristic of hypocellular interstitial fibrosis compatible with AAN. Of 45 glomeruli, 14 showed sclerosis change; the spared glomeruli showed normocellularity with marked wrinkling of capillary walls. The overall change is end-stage chronic interstitial nephritis consistent with AAN (Masson's trichrome stain, original magnification ×200.)

Discussion

Nephropathy caused by Chinese herb medicines first attracted attention when a report from Belgium during 1992–1993 was published [1]. The article described rapidly progressive interstitial renal fibrosis in nine young women who had followed a weight-loss regimen at the same medical clinic in 1992–1993. One year later, the presence of aristolochic acid (*fangchi*) instead of Stephania tetrandrine (*fangji*) in the pills was confirmed. This mistake had been made because of the similarity of the Chinese names *fangchi* and *fangji* [4]. Since that time, nephropathy caused by Chinese herb medicines has been reported in both western countries and Asian areas [5].

Aristolochic acid is the active substance extracted from *Aristolochia* spp. [6]. Aristolochic acid is a mixture of nitrophenanthrene carboxylic acids, which have two major components, aristolochic acid I (8-methoxy-6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid) and aristolochic acid II (6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid), and differ from each other by only one methoxy group. [6] Each component can be transformed into the other, depending on aerobic or anaerobic conditions. Aristolochic acid has been proven to be both nephrotoxic and carcinogenic. The carcinogenic and mutagenic effects associated with the binding of metabolites of aristolochic

acid to DNA have been extensively described and have resulted in the classification of aristolochic acid as a genotoxic carcinogen [7, 8]. The capacity to form specific DNA adducts reflects prior exposure to AA and involvement in pre-mutagenic lesion. The carcinogenicity of AA also suggests the need for developing screening strategies of urothelial carcinoma [8].

Aristolochic acid-associated nephropathy (AAN) is used to describe nephropathy caused by aristolochic acid-contaminated herbal medicines, and it is recognized as a separate entity of renal tubulo-interstitial disease. The renal pathology of interstitial fibrosis initially reported on the basis of a few renal biopsies has been integrated into a unique pathological finding: extensive hypocellular interstitial fibrosis with atrophy and loss of the tubules, which is predominantly located in the superficial cortex. Glomeruli were relatively spared, but some reports demonstrated global or peripheral sclerosis of glomeruli, decreasing from the outer to the inner cortex, including the columns of Bertin; severe fibromucoid to fibrous intimal thickening in interlobular and afferent arterioles; and thickening of Bowman's capsule [7].

The paucicellular interstitial fibrosis change may explain the clinical manifestation of severe anemia and rapid progressive renal failure observed in previous studies. Tubulotoxicity of AA has also been suggested in clinical investigations and confirmed in cultured cells [9, 10]. Tubular proteinuria, mainly β2-microglobulinuria and albumin, neutral endopeptidase enzymuria, and decreased megalin expression in cultured cells, suggested that impairment of proximal tubular function might be an early manifestation of AA toxicity in the kidneys [10]. In previous studies, Fanconi's syndrome seems to be a unique manifestation among Asian people with AAN [5, 11, 12]. Only one patient with AAN was reported to have Fanconi's syndrome in western countries. Fanconi's syndrome in the patient was reversible, and the patient recovered after discontinuation of the Chinese remedy [13]. Although AA was proven to be toxic to proximal cells, the correlation between AAN and Fanconi's syndrome remains controversial due to herbal concoctions in eastern countries [11]. In our patient, the manifestation of Fanconi's syndrome may imply that the proximal tubular cell is a primary target cell in AAN, or a consequence of herbal concoctions, since the boy had taken different kinds of Chinese herbs since early childhood.

Nephropathy caused by Chinese herbs also raises issues for public health authorities [14]. This problem is even more crucial in Asian areas, where people have been under the impression that traditional Chinese herb medicine is more natural and safer than western medicine and could be used for every health-related condition. Herbal drugs can be easily obtained from pharmacies and local markets without a doctor's prescription [15]. Parents play an important role in maintaining their children's health. Many oriental parents like to offer their children Chinese herbs to enhance their health. However, most herb preparations are not under strict scrutiny. If the Chinese herb mixture contains something nephrotoxic, it may endanger children with regard to terminal renal failure.

In summary, we described a 10-year-old boy who had ingested Chinese herbs containing aristolochic acid and at presentation had Fanconi's syndrome, severe anemia, and progressive renal failure that led to dialysis. The boy was diagnosed with AAN, a condition that has been discussed for a number of years in adults but has seldom been mentioned with regard to children. This case highlights the impact of misused Chinese herbs on children's health.

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