Case Report

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Acquired Fanconi Syndrome Induced by Mixed Chinese Herbs Presenting as Proximal Muscle Weakness

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We report a rare case with acquired Fanconi syndrome caused by mixed Chinese herbs, initially presenting as waddling gait and lower limb muscle atrophy. From a series of investigations, proximal renal tubule injury with functional defects and Chinese herb nephropathy were discovered. Hypophosphatemic osteomalacia and type II muscle fiber atrophy shown in muscle biopsy of left quadriceps may be associated with the sequelae of ingestion of mixed crude Chinese herbs. Aggressive and early alkali treatment with supplementation of phosphate and Vitamin D restored the patient's metabolic and musculoskeletal abnormalities.

Key Words
Chinese herb nephropathy;
Fanconi syndrome;
hypophosphatemia;
osteomalacia

Fanconi syndrome is a constellation of transport defects in the renal proximal tubule involving phosphate, calcium, potassium, bicarbonate, urate, amino acids and proteins. Acquired Fanconi syndrome can be caused by several factors and offending agents, among which Chinese herbal drugs have been demonstrated to be a remarkably causative source in recent years.[1,2] Intriguingly, most published literature about Fanconi syndrome caused by Chinese herbs are from East Asia.[3] Increasing interest has been raised in aristolochic acid, an herbal ingredient that may cause the prevailing presentations of hypokalemia paralysis, rhabdomyolysis and joint pain.[4] However, contaminated heavy metals and unidentified hazardous substances may lead to muscular injury and osteomalacia in adults in addition to the above-mentioned symptoms. Unless the physician keeps alert, the diagnosis of acquired Fanconi syndrome due to Chinese herbs may be overlooked, and further impeded in the presence of renal failure. Without early diagnosis and prompt management, irreversible musculoskeletal sequelae resulting from an imbalance of electrolytes may develop. We herein describe a young adult with acquired Fanconi syndrome initially presenting with waddling gait and proximal muscle weakness. These occurred 2 years after ingestion of crude traditional Chinese folk drugs for pain remedy. From a series of investigations, proximal renal tubule injury with functional defects and hypophosphatemic osteomalacia were discovered by meticulous differentiation.

CASE REPORT

A 32-year-old Chinese man was transferred to our Nephrology Division because of renal insufficiency, proteinuria and weakness of the bilateral thighs for ap-

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proximately half a year. Tracing his history, he had taken mixed folk remedies for an ankle sprain twice or 3 times daily for 2 years. Progressive body weight loss of 10 kg within a year accompanied by muscular atrophy of both thighs led to his difficulty in walking. He claimed that his renal function was normal prior to this event.

Physical examination disclosed blood pressure, 132/85 mmHg and pulse rate, 77 beats/min. Neurological examination indicated no limitation of extraocular movement, a muscle power test showed moderate proximal weakness in all 4 limbs and the scores of muscle strength over the lower extremities were $4^+/5$ with increased knee reflexes. No other neurologic manifestations were found. Routine laboratory data on admission showed hemoglobin, 8.7 g/dL, white cell count, 4,200/mm^3, platelet count, 162,000/mm^3, and urine pH 7.5, protein 30 mg/dL, glucose 0.5 g/dL, but negative for Bence-Jones protein. Biochemistry data for plasma and urine on admission revealed profound hypophosphatemia and hypouricemia with increased fraction excretion of phosphate and uric acid, as well as metabolic acidosis with a normal anion gap, serum creatine kinase, 33 U/L, lactate dehydrogenase, 113 U/L, alanine aminotransferase 7 U/L, glucosuria and non-nephrotic range proteinuria (Table 1). Thyroid function tests and plasma intact parathyroid hormone level were within normal limits. Immunologic surveys for autoantibodies were negative; tumor markers and serum complement levels were normal. Plasma and urine immunoelectrophoreses showed no evidence of monoclonal gammopathy. Serum ceruloplasmin level was 30 mg/dL (reference range: 22-58 mg/dL). Blood heavy metal analyses, including lead, copper, mercury, and cadmium, were within normal values.

Fanconi syndrome was established by the laboratory data (Table 1) and the proximal renal tubule defect in acidification. A $NaHCO_3$ loading test disclosed an increased fractional excretion of bicarbonate (27%) at a plasma HCO_3^- of 27 mEq/L and a urine-blood carbon di-

Table 1. Plasma and urine biochemistry data on admission and 1 month later

	On admission	1 month later	Reference range
Plasma			
pH	7.35	7.36	7.35-7.45
Na^+ (mEq/L)	140	140	135-147
K^+ (mEq/L)	3.6	4.1	3.5-4.7
Cl^- (mEq/L)	112	113	100-110
$HCO3^-$ (mEq/L)	16	20	22-24
Uric acid (mg/dL)	1.9	2.1	2.5-7.2
Inorganic phosphorus (mg/dL)	1.5	3.0	2.1-4.7
Glucose (mg/dL)	99	85	65-115
Blood urea nitrogen (mg/dL)	17	18	7-20
Creatinine (mg/dL)	1.8	2	0.7-1.5
Albumin (g/dL)	4.1	NA	3.7-5.3
Urine			
pH	7.0	6.0	-
Glucose (g/day)	7.41	NA	< 0.30
Protein (g/day)	0.38	0.28	< 0.15
Na^+ (mEq/day)	83.2	194.4	100-260
K^+ (mEq/day)	20.8	20.4	25-100
Urine anion gap*	16	NA	-
Phosphorus (mg/day)	290	290	400-1300
Uric acid (mg/day)	465.4	NA	250-750
Fraction excretion of phosphate (%)†	37	15	< 10
Fraction excretion of uric acid (%)‡	17	NA	< 12
Creatinine clearance (mL/min)	35	47	110-120

NA = not available. *Urine anion gap = urine ($[Na^+]+[K^+]-[Cl^-]$). †Fractional excretion of phosphate = $[(U_{PO4} \times P_{Cr})/(P_{PO4} \times U_{Cr})] \times 100$. ‡Fractional excretion of uric acid = $[(U_{UA} \times P_{Cr})/(P_{UA} \times U_{Cr})] \times 100$.

oxide gradient (ΔU-B P_{CO2}) of 45 mmHg at urine pH 7.6. Further investigations were done with regard to the patient's renal insufficiency and lower limb muscular weakness. Renal sonogram revealed normal kidney sizes and increased echogenicity without nephrocalcinosis in both renal cortices. Renal biopsy revealed diffuse interstitial fibrosis with hypocellular inflammatory infiltration, but preserved glomeruli of the ischemic shrinkage (Fig. 1). A needle electromyographic study at right rectus femoris, gastrocnemius, biceps brachii, triceps brachii and mid-thoracic paraspinalis disclosed an increase of insertional activity and spontaneous activities. Recruitment was normal all over. A nerve conduction study was normal on both motor and sensory nerves of legs. Muscle biopsy from the left quadriceps further showed mild type II muscle fiber atrophy, but inflammatory myopathy with cell infiltration and phagocytosis was not found. Bone mineralization density measured by dural energy X absorptiometry revealed low bone mass and mild osteoporosis of WHO criteria grade 1. No pseudofracture line was noted from the skeletal plain films.

Initially, the patient was treated with oral neutral phosphate (4.5 g, twice a day), $NaHCO_3$ and active vitamin D_3 (0.25 μg, once a day). Muscle weakness of the lower limbs was alleviated dramatically 4-5 days later. The serum level of phosphate and acidemia improved (Table 1), then were normalized 6 months later. His anemia responded to subcutaneous recombinant human erythropoietin therapy (6,000 IU/week) and the overall quality of life improved substantially. Nevertheless, his renal function remained stationary in spite of cessation of the Chinese herbs for 6 months.

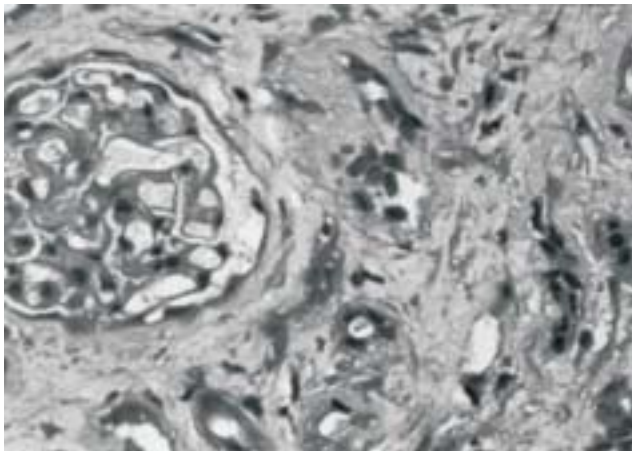

Fig. 1. Renal biopsy revealed diffuse interstitial fibrosis with tubular atrophy (> 30% of cortical parenchyma involvement) and ischemic shrinkage of glomeruli (H & E stain, × 500).

DISCUSSION

A growing body of evidence has shown that rapidly progressive nephropathy is caused by crude traditional Chinese drugs.[1,5] Moreover, crude traditional Chinese drugs have recently been implicated in the genesis of acquired Fanconi syndrome.[6] Our case displayed the prevailing symptoms with proximal muscle injury and evident osteomalacia associated with hypophosphatemia, which differed from previous reports.[1,2,4] Although bone biopsy was not performed in our patient, osteomalacia was highly suspected in the presence of hypophosphatemia with increased serum level of alkaline phosphatase, as well as a loss of bone density measured by dural energy X-ray absorptiometry. Furthermore, other metabolic bone diseases were excluded and parathyroid hormone level was normal in our case.[7] An improvement in muscle power following phosphate supplementation, correction of acidemia, and less brisk knee joint reflexes provided the evidence for our suspicions.

Proximal renal tubular acidosis is usually found in Fanconi syndrome,[8] though a defect of distal acidification sometimes supervenes. Our patient exhibited normal anion gap metabolic acidosis with hypophosphatemia, hypouricemia, glucosuria and a normal blood sugar level. Increased phosphates and uric acid fractional excretions declared the origin of renal loss. A bicarbonate titration test further clarifies the proximal tubular defects in our patient.[9] Several acquired causes of Fanconi syndrome, such as Wilson's disease, autoimmune disease, monoclonal gammopathy, and heavy metals were excluded. Based on the pertinent history of the use of crude traditional Chinese drugs and the unique pathological findings of interstitial nephritis with spared glomeruli in our case, it is reasonable to link the Chinese herb nephropathy with the acquired Fanconi syndrome and musculoskeletal sequelae.

Since crude traditional Chinese drugs have been associated with tubulointerstitial fibrosis and acquired

Fanconi syndrome, there might be some unusual physiochemical properties of herbal drugs that exhibit a distinctive ability to alter proximal tubular transports. The endocytic receptors megalin (gp330) and cubulin are located on the lumen surface of the renal proximal tubule epithelium, where they mediate the uptake of a wide variety of protein ligands for glomerular filtrate. Normal reabsorption of glomerular filtrated proteins probably requires recycling of the endocytic receptors megalin and cubulin. The defective trafficking of megalin involves the pathogenesis of some cases of Fanconi syndrome, *i.e.* Dent's disease and Lowe's syndrome.[10] Besides, the ClC-5 chloride channel is likely to be located in recycling endosomes, and may form part of the receptor-mediated endocytic pathway that reabsorbs low-molecular-weight proteins and albumin.[10] In Fanconi syndrome, urinary megalin deficiency was implicated in abnormal tubular endocytic function.[11] Therefore, it is speculated that the endocytosis process might be impaired by the accumulation of some components of crude traditional Chinese drugs. Furthermore, the clogging of the endosomal system might alter apical membrane recycling or cause direct toxicity to the ClC-5 chloride channel. However, we need more molecular biological studies to validate whether the endocytosis trafficking defect plays a role in the pathogenesis of Fanconi syndrome induced by the herbal drugs.

To date, many crudely mixed traditional Chinese drugs with unknown components toxic to the kidney are widely used in the world. They are popular for many reasons, such as slimming, building body strength, relieving intractable pain and impotence. In this report, we draw attention to the diverse clinical manifestations of acquired Fanconi syndrome associated with Chinese herbs. When confronted with a patient with proximal muscle weakness and recent exposure to Chinese herbal drugs, the physician should be alert for reversible tubular damage and remediable electrolyte changes.

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