Case Report

REVERSIBLE ACUTE RENAL FAILURE DUE TO CHINESE HERBS

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ABSTRACT

Recently, herb induced nephropathy has been described as a subgroup of renal disorders. Patients taking Chinese herbs for eczema and weight reduction have been reported to develop chronic interstitial nephritis, rapidly progressive interstitial fibrosis and urothelial malignancies. An agent, known as aristolochic acid (AA), isolated from such herbs has been identified as an independent and direct nephrotoxin. The pathology by which AA incurs renal damage is yet to be determined. With regards to malignancies triggered by such herbs, these patients have been found to over express a mutated p53 gene.

Here, we discuss the management of a young female patient who developed biopsy proven acute interstitial nephritis with early fibrosis after ingesting a herbal remedy for a short period of time. Other causes of interstitial nephritis in this patient such as viral infections and autoimmune disorders were investigated and ruled out. Initially, she presented with acute renal failure requiring hemodialysis for ten days. Fortunately, she did not develop any permanent renal dysfunction as the etiology was identified early and the herbs were discontinued immediately. Her renal impairment reversed to normal within a one-month period after a trial of corticosteroids was administered. We believe this is the first of such cases isolated in Saudi Arabia.

KEY WORDS: Chinese herbs, Aristolochic acid, Interstitial nephritis, Steroid therapy.

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INTRODUCTION

Various studies have showed the relationship between Chinese herbs and renal disease. This could take the form of chronic interstitial nephritis, rapidly progressive fibrosing interstitial nephritis or renal malignancy.[1-5] The aristolochic acid contained in these herbs is blamed for the above pathologies. The cumulative dose of aristolochic acid is a significant risk factor in these patients; particularly if it exceeds 200 grams, there is a higher risk for urothelial malignancy.[6]

Here we describe a case of a young female who consumed Chinese herbs for a short time and presented with acute renal failure (ARF). The biopsy showed acute interstitial nephritis with early fibrosis. Cessation of the herb with administration of corticosteroids resulted in a full recovery. She required dialysis for ten days but her renal function returned to normal after one month of steroid therapy.

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We believe this is the first case reported in Saudi Arabia with such a presentation. We also believe that if the etiology of her renal dysfunction was not determined early, this lady may have progressed to chronic renal failure.

CASE REPORT

A 23-year-old Indonesian female, residing in Saudi Arabia, was admitted to King Abdulaziz University Hospital through the ER with a three-day history of nausea and vomiting. The vomitus contained food particles and there was no hematemesis nor was the vomiting projectile. It was associated with left upper abdominal pain that was dull in nature and of severe intensity. It was also associated with watery diarrhea. She did not note any blood or mucous in her stools nor did she complain of accompanying tenesmus. However, she noticed a decrease in the volume of her urine during this same time period. There was no dysuria and the color of the urine did not change. Two days later she developed a high-grade fever with chills, rigors, and sweating. She denied eating food other than homemade food. She gave no history of recent travel or contact with any ill patient. A week prior to presentation, she had taken a sachet of herbal medicine for generalized fatigue. However she did not take any other medication, in particular, no antibiotics or analgesics were ingested. Her review of systems including musculoskeletal, respiratory, and neurological was non-revealing. She had no past medical or surgical illnesses and was never admitted to a hospital before. No member of her family suffered any gastrointestinal, rheumatological, or renal diseases. She is married, does not smoke or consume alcohol, and works as a housemaid.

At presentation, she was conscious and oriented. Her vital signs were as follows:

T	:	36.4	°C
P	:	90	bpm
BP	:	110/70	mmHg
RR	:	20	/min

Generally, she was pale and jaundiced. She had no stigmata of chronic liver disease, no lymphadenopathy, no rashes, no arthritis, no oral ulcers, and no alopecia. Her cardiovascular, chest, and neurological examinations were all within normal. Examination of her abdomen only revealed generalized tenderness.

Her laboratory investigations are summarized in Tables-I, II, III and IV. As her hemoglobin dropped from 12.5 to 5.7g% (Table-I) and her stool revealed occult blood on two separate occasions, an esophagogastroduodenoscopy was performed. No abnormal findings were detected. Hematological tests showed no evidence of hemolysis. Her coagulation profile showed an initial disturbance and later improved (PT of 2 on admission compared to 1.1 on 14/01/01 and PTT of more than two minutes on admission compared to 39 seconds on 14/01/01). An ultrasound of the abdomen was performed and illustrated a normal sized liver with a coarse homogenous echo pattern. The kidneys were both of normal size, outline and shape. They were diffusely echogenic and the corticomedullary differentiation was preserved. There was no evidence of stones or hydronephrosis. Her urine culture grew E. coli for which she received a ten-day course of erythromycin and cefuroxime. Blood cultures were negative repeatedly and a stool culture revealed Salmonella Enteritidis which required

Table-I: CBC

	31/12/00	01/01/01	08/01/01	13/01/01	18/01/01	24/01/01	31/01/01
WBC	27.1 (91% Neut)	16.2 (89% Neut)	13.7 (74% Neut)	10.7 (68% Neut)	5.77 (53% Neut)	9.39 (84% Neut)	17.3 (83% Neut)
Hb	12.5	11	9.06	7.47	5.7	9.7	9.2
Plt	105	79.2	467	524	404	353	449

Table-II: U & E, mmol/l

	31/12/00	*03/01/01*	*06/01/01*	*08/01/01*	*14/01/01*	*16/01/01*	*22/01/01*	*27/01/01*	*03/02/01*	*04/02/01*	*18/02/01*
Na	134	138	130	132	136	133	130	137	134	134	143
K	4.4	4.4	4.8	4.6	4	4.3	4.3	4.7	4.1	4.8	3.4
BUN	27.7	31.1	30.3	23.9	6.4	8.5	17.1	41.6	26.5	23.8	4.6
Creatinine	623	914	1144	1113	619	756	658	650	317	297	104

no treatment as her diarrhea subsided immediately after hospitalization and she showed no laboratory evidence of microangiopathic hemolytic anemia.

During hospitalization, she remained oliguric (urine output ranged form 200-300cc/24 hours), she became fluid overloaded, her BUN and creatinine were gradually increasing (Table-II) and her bicarbonate decreased from 21.2 on admission to 13 on 03/01/01. Accordingly, hemodialysis was started. After her coagulation profile was corrected with fresh frozen plasma, she underwent a kidney biopsy on 16/01/01. The biopsy demonstrated the following:

* The glomeruli exhibited a very mild increase in the mesangial cells & matrix. No sclerosis, synechia, or adhesions were visualized.
* The interstium showed an increase in the chronic inflammatory cells and few eosinophils with mild interstitial fibrosis and interstitial infiltrate.
* Mild atrophy of the tubules was noted.
* Immunofluorescence was negative for Ig A and C_4 and was positive for Ig G, Ig M, and C_3.
* A Diagnosis of Acute tubulo-interstitial nephritis with Eosinophils was made.

On her 19th day in hospital, she began to diurese and subsequent serial chemistry tests showed a steady decline in the creatinine level (Table-II). On day 21, hemodialysis was discontinued. Prednisolone was started at a dose of 60mg/ day. Her U&E's and urine output (Table-III) continued to be monitored. With remarkable improvement in symptoms, urine output and chemistry, prednisolone was tapered off after two weeks and she was discharged from the hospital to be followed up in the outpatient clinic. Three weeks later, her serum creatinine had decreased to 54mmol/L.

DISCUSSION

Many causes of interstitial nephritis, whether acute or chronic, have been identified. Since the early 1990's herb-induced tubulo-interstitial disease has been recognized as a growing entity. The first of such reported cases came from Belgium in 1991 when 14 women at a weight reduction clinic presented with advanced renal failure secondary to biopsy proven chronic tubulo-interstitial nephritis.[3,7,8] By 1999 more than 100 cases had been identified a third of whom required renal transplantation. A compound, aristolochic acid (AA), incorporated in herbal preparations used in this clinic and other clinics in the UK, France, Japan, and Taiwan for weight reduction, "promoting health", and eczema, was implicated as the causal agent.[4-6,9] This compound was extracted from a plant called Aristolochia Fang Chi. This nephrotoxin replaced the previously used Stephania tetranda herb.[5] AA is believed to primarily induce extensive cortical interstitial fibrosis with minimal cellular infiltrate as well as tubular atrophy, which accounted for the low-grade proteinuria and glycosuria giving a picture of Fanconi Syndrome in some reported cases.[9] Furthermore, thickening of

Table-III: Urine output, ml/day

24/01/01	*25/01/01*	*26/01/01*	*29/01/01*	*30/01/01*	*02/02/01*	*03/02/01*	*04/02/01*	*05/02/01*
1150	1750	975	1900	2900	1400	1000	2000	1500

Table-IV: Other laboratory tests

Hematologic Tests	
Malaria film	Negative
Cold Agglutinins	Negative
S. Iron & Ferritin	Normal
Cultures	
Blood culture	Negative
Urine culture	E coli sensitive to cefuroxime
Stool culture	Salmonella Enteritidis
Immunologic Testes	
HBc Ig M	Negative
HBs Ag	Negative
HAV Ig M	Negative
HCV Ab	Negative
HIV	Negative
CMV Ig G	Negative
CMV Ig M	Negative
Parvo 19 Ig G	Negative
EBV Ab's	Negative
Ig E	3543
C_3	0.656 (n 0.75 – 1.65)
C_4	0.18 (n 0.3 – 0.6)
ANA	1:40
RF	Negative
Antismoothmuscle Ab	Negative
Antimitochondrial Ab	Negative
c and p - ANCA	Negative
Stool Analysis	+ occult blood
Urinalysis	2+ protein 1+ glucose 3+ occult blood 3-6 RBC/hpf 1-3 WBC/hpf

interlobular and afferent arterioles due to swelling of endothelial cells occurred. This finding suggests that the primary lesion is in the vessel walls, which subsequently leads to ischemia and fibrosis of the interstitium. The glomeruli, however, were minimally involved with tuft collapse and wrinkling of Bowman's capsule but there was no evidence of glomerulonephritis. These pathological findings have been demonstrated in thirty-three patients biopsied in Belgium and reproduced in the UK and other countries. This suggests that herb-induced nephropathy produces characteristic pathological changes.[3,5,7,8]

In addition to interstitial fibrosis, other reports noted the development of urothelial cellular atypia, carcinoma in situ and even transitional cell carcinoma (TCC). The carcinogenic effect of AA involves over expression of a mutated p53 gene.[1,10] Some patients in Belgium with herb-induced nephropathy who had undergone transplantation had their native kidneys and ureters removed. Urothelial lesions in the form of atypia and in the form of TCC in situ were detected in 100% and 40% of these patients respectively.[1] The exact role of AA in the p53 gene mutation is yet to be delineated. It has not been established yet whether patients exposed to AA, but have not suffered from herb nephropathy, are still as risk of developing urothelial malignancies.

Despite all the incriminating reports on AA, the pathogenesis of the nephropathy is not fully understood. Uncertainties revolve around characteristics of the individuals at a higher risk of developing AA nephropathy. That is, not all those consuming AA develop nephropathy. For example, it has been observed that women develop renal disease after exposure to AA more often than men. A number of other confounding variables have been questioned including toxin dose, batch-to-batch variability, genetic predisposition, and individual differences in toxin metabolism.[2] Interestingly, it has been noticed that patients in Germany receiving AA as a component of immunomodulatory drugs in concentrations equal to or more than that of herbal remedies were not reported to develop nephritis. This observation prompted analysts to conclude that progressive tubulo-interstitial fibrosis is a consequence of a combination of agents. That is, fenfluramine and diethylproprion (appetite suppressants), frequently used in combination with herbal remedies in slimming clinics, cause renal vasoconstriction, which may potentiate the nephrotoxic effect of AA.[2] Other scientists substantiated their hypothesis of an independently AA-induced nephropathy by taking

renal tissue from five patients with herb nephropathy and six patients with other renal diseases. They retrieved AA-derived DNA adducts from all five cases with herb nephropathy and found no trace of this biomarker in the six controls. Thus, they confirmed the direct and independent nephrotoxic effect of aristolochic acid.[11]

At this point, it is important to consider the clinical implication of such nephropathy. Most reported patients presented with renal insufficiency typical of tubulo-interstitial disease. That is, the urinary sediment revealed only a few RBC's and WBC's with moderate protein excretion. The serum creatinine ranged from 123-1122mmol/l, the blood pressure was normal or mildly elevated, and early severe anemia developed.[2-9] This progressive renal impairment warranted dialysis and renal transplantation in a significant number of patients.[1-3,5,7,8,10] It has been extrapolated that the progression of insufficiency increases with the duration of use.[2] Some individuals continue to deteriorate even after herbal remedies are discontinued. In such cases use of corticosteroids to slow the rate of renal loss has had a debatable outcome. Some argue that the hallmark of the disease is fibrosis without prominent inflammation, thus the efficacy of corticosteroids will be limited.[2] Yet, a study done on 12 Belgian women with biopsy proven fibrosis demonstrated that steroid use at a dose of 0.1mg/kg every two weeks for one year resulted in a steeper decline in serum creatinine levels compared to the control group. Furthermore, a smaller number of patients required dialysis at one year after use of steroids. This may suggest an immune mediated mechanism of renal injury.[12]

With regards to our patient, she consumed the herb for a short period of time (one week). Her biopsy revealed early fibrosis with minimal inflammation of the interstitium, atrophy of the tubules, and limited glomerular involvement, which is pathgnomonic of herb-induced nephritis. Aside from her biopsy, examination of her urine was consistent with tubular dysfunction and there was no indication of glomerular disease, i.e. few WBC's and RBC's as well as proteinuria and glycosuria and no detectable casts. In spite of all our attempts at investigating for other causes of nephritis such as SLE, no cause could be found (Table-IV). The autoimmune profile, malaria film, brucella titers, viral studies, etc. were all negative. In addition, there was no history of any other drug ingestion such as analgesics or antibiotics that could be incriminated as the causative agents in this patient. Even the rapidly progressing fibrosis characteristic of herb-induced nephritis leading to an equally rapid deterioration in renal function was observed in this young lady. Her disease continued to progress in-hospital as marked by the rising creatinine (from 623 mmol/l on admission to 1144mmol/l at the start of dialysis), worsening acidosis (the bicarbonate dropped from 21.2 to 13) and fluid retention eventually mandating hemodialysis. She also developed acute severe anemia, which was attributed to her renal disease. Her Hb decreased from 12.5 to 5.7g% within a two-week period (Table-I). Her coagulation profile did not demonstrate a DIC picture nor was there evidence of hemolysis. An upper GIT endoscopy was performed and ruled out acute blood loss. However, because the duration of use of this herb was short, we anticipated a good prognosis for our patient. And indeed, the creatinine level stabilized, the urine output improved (from 200-300cc/24° to 975-2900cc/24°) and her symptoms, namely the nausea and vomiting, disappeared. She was given the benefit of the doubt, and a trial of prednisolone at a dose of 60mg/day was administered for two weeks after which it was tapered off gradually.

We believe that the herbs may have triggered an autoimmune allergic reaction in the kidneys of this lady that could have progressed to end stage renal disease if the diagnosis was not made early or if she continued to consume the herbs. We looked carefully for any other cause for interstitial nephritis but no etiology was found except the herb particularly when considering that she did not take any other medication, and there was no evidence of any viral

infection. We think the disturbed liver function tests and disturbed coagulation was mainly related to sepsis originating from the urine. The urine culture grew E. coli for which she received both erythromycin and cefuroxime. Her blood culture was negative on more than one occasion. Her stool revealed Salmonella Enteritidis, yet a hemolytic uremic syndrome secondary to Salmonella or E.coli was unlikely as there was no evidence of microangiopathic hemolysis.

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