

## Acute Kidney Injury Due to Arsenic Contained in Alternative Medicines in the Setting of Adult Nephrotic Syndrome

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### Background

Potentially toxic levels of heavy metals like lead, arsenic have been found in alternative medicines manufactured in India. Given the widespread use of these preparations, their nephrotoxicity is likely to be common. Unexplained renal failure; therefore should always be evaluated for the possibility of heavy metal nephrotoxicity due to alternative drugs. We report here a case of acute kidney injury that occurred in an adult with nephrotic syndrome which was the result of arsenic nephrotoxicity following consumption of ayurvedic medicines.

### Case History

33 year old male presented to us with history of puffiness of face, edema feet of 2-3 weeks duration. 4-5 days before admission he developed oliguria with worsening of edema. There was no history of fever, upper respiratory tract symptoms, pyoderma, or jaundice preceding the illness. He also denied any history of hematuria, flank pain, prior similar episodes or recent NSAIDs use. His past history was significant for use of unlabeled alternative ayurvedic powder and liquid for eczematous skin lesions for last 6 months.

On evaluation, he was afebrile, conscious, and alert with heart rate of 86 per minute, blood pressure 114/66 mmHg with no postural drop. He had edema upto knees and there was no pallor, lymphadenopathy, skin hyperpigmentation, nail changes, or icterus. Chest was clear to auscultation, heart sounds were normal, there was no hepatosplenomegaly. Higher mental functions were normal and there was no evidence of peripheral neuropathy.

Laboratory evaluation showed: Hemoglobin 13.4 g/dl, leucocyte count of 11300 (with 68% polymorphs and 22% lymphocytes), platelets 2,33,100/cmm, Urine albumin 4+, no red blood cells, occasional pus cells and granular casts. 24 hr urine protein 4.2 gm/day, blood urea nitrogen 16mg/dl, creatinine 1.6mg/dl, total protein 5.5 g, albumin 2.4 g, sodium 132 mEq, potassium 3.8 mEq, chloride 101 mEq, serum total cholesterol 412 mg and triglyceride 344 mg/dl. Serologies for antinuclear antibodies and anti double stranded antibodies were negative and complement C3 and C4 levels were normal. A kidney biopsy was performed and in view of history of consumption of alternative medicines, samples of ayurvedic powder and liquid were sent for toxicological analysis.

After admission patient remained oliguric and there was no response to volume expansion with 200 ml of 10% albumin with diuretics. Serum creatinine rose to the peak of 3.7 mg/dl. Patient was treated conservatively as a case of nephrotic syndrome with acute kidney injury. Renal replacement therapy was not required. After 8 days of oliguria patient went into diuretic phase and creatinine decreased to 1.1 mg/dl on day 14 of admission.

Kidney biopsy showed predominant involvement of tubulointerstitium with glomeruli showing normal basement membrane and cellularity. Tubule showed denudation of epithelium and fraying of borders. Interstitium showed deposition of pink, rectangular, and polarizing crystals extending at places into the tubular epithelium and

lumina along with sprinkling of lymphocytes. Immunofluorescence was negative for immune deposits. Electron microscopy showed diffuse foot process flattening consistent with minimal change disease.

Toxicological analysis of alternative medicine showed very high content of arsenic-232 microgram ( $\mu\text{g}$ ) per gram along with elevated blood level of arsenic at 54  $\mu\text{g}/\text{dl}$  (normal limit 0.17-5  $\mu\text{g}/\text{dl}$ ). Blood lead levels were normal (10.2  $\mu\text{g}/\text{dl}$ ).

Patient was treated with prednisolone 1 mg/kg/day (55mg/day), to which he promptly responded and went into remission in 2<sup>nd</sup> week of therapy. 4 years following the first episode patient suffered one relapse (steroid responsive) and is at present in complete remission.

Given the clinical, laboratory, and histopathological findings- patient suffered acute tubular necrosis with interstitial nephritis as a result of crystallopathy due to arsenic contained in ayurvedic drugs.

### Discussion

Acute renal failure is more commonly seen in adult nephrotic syndrome and etiologies include hypovolemia causing prerenal azotemia (and if untreated acute tubular necrosis), drug induced interstitial nephritis, nephrosarcoma, bilateral renal vein thrombosis etc. [1,2] Although diuretics, NSAIDs, antibiotics are common causes of acute tubulointerstitial nephritis in this setting- alternative medicines marketed in India should be an important addition to this list. Their use is common and often not recognized as a cause of drug induced renal failure (ayurvedic preparations are commonly advertised as being free of side effects).

To our knowledge, this is the first report of acute kidney injury caused by alternative drugs in the setting of adult nephrotic syndrome. Although blood levels of arsenic are maintained normal even in the

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setting of acute toxicity due to prompt renal excretion, this may not hold true in nephrotic state in which glomerular filtration rate is often low [2]. This explains high blood levels of arsenic in our patient. Predominant renal involvement without other systemic feature of arsenic toxicity such as skin rashes, peripheral neuropathy is also an unusual feature in our case. This can be explained on the basis of kinetics of arsenic after ingestion. After ingestion arsenic is well absorbed from gastrointestinal tract and is taken up by red blood cells for distribution throughout the body. Trivalent arsenic (+3), the most toxic form, avidly binds to sulfhydryl groups (proteins, glutathione, cysteine) and interferes with numerous enzyme systems [3]. Tubular loading with filtered proteins in nephrotic syndrome is postulated amongst one of the mechanisms of tubular injury in this setting [4]. If this is true, it is possible that if a nephrotic patient is exposed to arsenic, it will be selectively taken up by tubular epithelium along with filtered proteins to which trivalent arsenic preferentially binds. Thus nephrotic syndrome may predispose to arsenic nephrotoxicity.

Studies have previously demonstrated alarmingly high heavy metal content in alternative medicines marketed from India [5,6]. There use is highly prevalent in India where bulks of primary care physicians belong to alternative medicine disciplines like ayurveda, homeopathy, unany etc. Physicians should specifically enquire about consumption of such preparations when confronted with unexplained renal failure. Heavy metal analysis of these drugs should be a routine in this setting.

Regulations from drug controller authorities regarding use of such preparations are urgently required.

## Conclusions

Heavy metal nephrotoxicity is an important differential diagnosis of acute kidney injury associated with nephrotic syndrome. Thorough history, clinical, toxicological evaluation, and prompt withdrawal of alternative medicines are necessary for successful outcome.

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