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BRIEF COMMUNICATION

NEPHROLOGY WILEY

Traditional medicines prescribed for prevention of COVID-19: Use with caution

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Abstract

Acute interstitial nephritis can result due to exposure to any medication, toxins, infections or malignancy. In the midst of this Coronavirus (COVID-19) pandemic, there has been a race for finding remedies to prevent the spread of and control the complications due to Severe Acute Respiratory Syndrome Coronavirus 2. Certain Indian medicinal herb concoctions like kabasura kudineer and nilavembu kudineer are being widely publicized to boost immunity and reduce the risk of developing COVID-19. Little knowledge exists about the adverse effects of these herbal remedies. We report two patients who presented to us with vague complaints following the ingestion of kabasura kudineer and we diagnosed them with acute tubulointerstitial nephritis (ATIN). The temporal relationship of ingestion of these remedies to the development of ATIN calls for vigilance and caution with regular monitoring of renal functions especially in those with chronic kidney disease.

KEYWORDS
acute kidney injury (AKI), COVID-19, herbal medications

SUMMARY AT A GLANCE

Summary At A Glance: Certain herbal medicines are being prescribed to boost immunity and reduce the risk of developing COVID-19 in India. Little is known about the adverse effects of these herbal remedies. This study reports the nephrotoxicity of the Kabasura Kudineer formulation which calls for attention to potentially serious adverse effects of some alternative medicine.

1 | INTRODUCTION

The COVID-19 pandemic, which first reported in Wuhan, China, has now more than 10 million people infected worldwide. Various therapeutic strategies are being researched, and trials are being done to find the prevention and cure for this deadly virus. Traditional Indian systems of medications which include Siddha have also offered a variety of herbs to improve immunity to prevent the development of COVID-19. Official Siddha formulations kabasura kudineer chooranam is believed to be a potent formulation with anti-viral and immuno-modulatory properties.[1,2] We report two patients who developed acute kidney injury (AKI) following the consumption of this formulation.

2 | CASE HISTORY

2.1 | Patient K

Mr K, a 51-year-old male who had an aortic valve replacement in 2013 presented with loss of appetite and easy fatigability of 1-week duration.

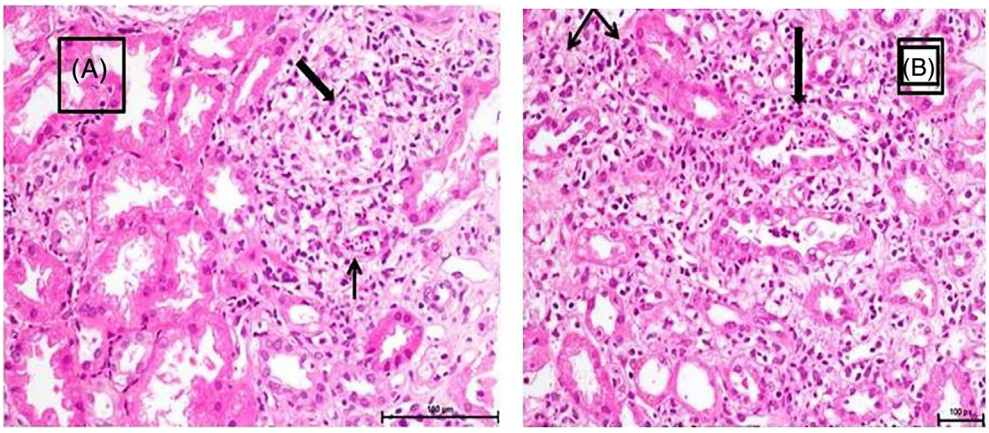

FIGURE 1 (A) Interstitial inflammation with tubular injury and WBC cast (H&E). (B) Tubular injury with neutrophilc tubulitis and WBC cast; interstitial edema and inflammation (H&E)

He reported no history of diabetes or hypertension. His medications included warfarin and nebivolol. He had no fever, rash, joint pains, cough, or hemoptysis. He had not consumed any known nephrotoxic agents like antibiotics, non-steroidal anti-inflammatory drugs or proton pump inhibitors (PPI). On further questioning, he said that he was taking 'kabasura kudineer' 60 ml once a day a week prior to the start of his symptoms. His baseline serum creatinine (SCr) done 2 months prior was 1.1 mg/dl. At presentation, he was euvolemic and had a blood pressure of 120/70 mmHg. His urinalysis showed no proteinuria but sediment revealed 3–5 WBC/HPF, 10–15 RBC/HPF and many granular casts. Mid-stream urine culture was sterile. Serum creatinine at presentation was 2.8 mg/dl and international normalized ratio was 2.4. Ultrasound showed normal sized kidneys with no hydronephrosis. After stopping warfarin and the herbal drink for 5 days, a kidney biopsy was performed as serum creatinine was still 2.8 mg/dl. Renal biopsy revealed acute tubulointerstitial nephritis (ATIN) in the background of mild arteriosclerosis, immunofluorescence (IF) was negative (Figure 1A). He was started on 0.5 mg/kg/day of prednisone. SCr after 2 weeks is 1.3 mg/dl and steroids were tapered by 5 mg every 5 days. Three months later his SCr remains at 1.2 mg/dl.

2.2 | Patient D

Mr D, a 63-year-old male with no known co-morbidities presented with nausea of 1-week duration. He was on no medications except for kabasura kudineer around 30–40 ml twice a day for 2 days prior to the symptoms. He had not consumed any known nephrotoxic agents like antibiotics, NSAID or PPI. At presentation he was anaemic, euvolemic and had a blood pressure of 140/70 mmHg. He was afebrile with no rash or joint swelling. He did not have any baseline blood tests done prior to this episode. SCr was 3.8 mg/dl, haemoglobin 7.2 g/dl and urinalysis showed many WBC and WBC casts. Mid-stream urine culture was negative and ultrasound showed normal sized kidneys. Renal biopsy was performed which showed ATIN on a background of early IgA staining on IF (Figure 1B). He was started on 0.5 mg/kg/day of prednisone after confirming a normal gastroscopy. The serum SCr decreased to 2.8 mg/dl a week later. He was tapered off the steroids over 6 weeks and his serum creatinine after 2 months is 1.1 mg/dl.

The details of the both the patients are illustrated in Table 1.

3 | DISCUSSION

Acute kidney injury with ATIN can occur due to numerous prescribed and over-the-counter medications and health drinks. It is estimated that one in three cases of ATIN can be due to endogenous and exogenous toxins. Establishing the causality of health food & health drink toxins inducing kidney disease is a challenge and requires a detailed history, time course, assessment of competing risk factors, and mechanism of injury and biological plausibility of the toxins.

Kidney toxicity of the agent and underlying patient characteristics such as increasing age, alter the metabolism and pathway of excretion of various agents administered and enhance the risk of the development of ATIN.[3] The National Kidney Foundation has cautioned against the use of herbal supplements and drugs without adequate monitoring as vulnerable populations like those with chronic kidney disease (CKD) can suffer significant damage.[4,5] The kidneys which are involved in the elimination of xenobiotics, environmental agent and metals through glomerular filtration, tubular secretion and metabolism is highly vulnerable to the toxicity of these agents.[6]

Siddha system of medicine, one of the oldest systems of medicine, has been promoting 'kabasura kudineer', as a formulation for immunity building affecting tumour necrosis factor signalling pathways.[7] It contains 16 constituents (*Zingiber officinale*, *Piper longum*, *Syzygium aromaticum*, *Cirucirukancori ver*, *Tragia involucrata*, *Anacyclus pyrethrum*, *Solanum anguivi*, *Terminalia chebula*, *Justicia adhatoda*, *Coleus aromaticus*, *Saussurea costus*, *Tinospora cordifolia*, *Clerodendron serratum*, *Andrographis paniculata*, *Cissampelos pareira*, *Cyperus rotundus* and neer [water]). It has been recommended to mix 8 g of the powder in four glasses of water and boil to reduce it to a glass and to be taken two to three times a day. Active phytoconstituents of this polyherbal decoction is supposed to have high affinity to the spike protein of the COVID-19 virus and hence prevents its binding to the ACE2 receptor on the host cell.[7,8] Among the constituents, *Syzygium aromaticum*,[9] *Solanum anguivi*,[10] *Andrographis paniculata*[11] and *Cyperus rotundus*[12] have been known to produce various degrees of nephrotoxicity according to case reports and series.

TABLE 1 Clinical characteristics of the patients

Name	Mr. K	Mr. D
Age	51 years	63 years
Gender	Male	Male
Base line serum creatinine [SCr (mg/dl)]	1.21 mg/dl in January 2020	Not available
Diabetes mellitus	No	No
Systemic hypertension	No	No
Others	S/P. Aortic valve replacement (January/2013)	None
Medications	Warfarin and metoprolol	None
Urine routine	Albumin-nil, sugar-nil, pus cells 3–5, epithelial cells 1–2, RBC 10–15, granular cast present	Albumin-nil, sugar-nil, Pus cells >50, epithelial cells 2–3, RBC 3–5, WBC cast and granular cast present
Haemoglobin (g/dl)	12.9	7.2
Total leucocyte count (cells/mm^3)	18 300	8900
Platelet (Lak/mm^3)	3.00	3.18
Urea (mg/dl)	29	74
SCr at presentation (mg/dl)	3.56	3.25
Sodium (mmol/L)	138	124
Potassium (mmol/L)	3.47	2.89
Bicarbonate (mmol/L)	29	30
Calcium (mg/dl)	8.6	8.4
Phosphorous (mg/dl)	3.2	4.4
T. protein (g/dl)	10.3	6.5
Albumin (g/dl)	4.7	3.4
TSH (mIU/L)	3.22	1.95
HbA1c (%)	5.6 (23 December 2019)	6.3
Oro pharyngeal Swab for RT-PCR COVID	Negative	Negative
Kidney biopsy Findings	Acute tubulointerstitial nephritis Mild to moderate Arteriosclerosis Interstitial fibrosis and tubular atrophy 10%–15%	Acute tubulointerstitial nephritis IgA nephropathy Interstitial fibrosis and tubular atrophy 5%–10%
Immunofluorescence	Negative for IgA, IgG, C3, Kappa and Lambda	IgA (2+), C3 (Trace), Lambda (2+) and Kappa (Trace)
Treatment given	Prednisone 0.5 mg/kg bodyweight/day tapered over 8 weeks	Prednisone 0.5 mg/kg bodyweight/day tapered over 6 weeks
SCr (mg/dl) after 2 weeks of treatment with steroids	1.49	2.23
SCr (mg/dl) on further follow up	1.2 mg/dl after 3 months	1.1 mg/dl after 2 months
Side effects of treatment	Hyperglycemia needing medications	Hyperglycemia needing medications

To the best of our knowledge, ATIN due to 'kabasura kudineer' has not yet been reported. We referred to the criteria by Naranjo et al.[13] to report an adverse drug event. A score of 6 was derived using these criteria, rating this adverse reaction as "probable". Nephrotoxicity was attributed to this drug on the basis of the criteria of Naranjo et al., clinical onset of AKI, absence of any other nephrotoxic drugs being administered, and histopathological findings on the renal biopsy.[13] In our two patients, the temporal relationship to kidney injury with no previous known nephrotoxic agents establishes a cause and effect relationship. The ATIN seems to be dose independent as both the patients took different amounts of the drug and the time period to the development of AKI has also been variable. Interestingly both had gastrointestinal symptoms after taking the formulation. It is worthwhile to think both these patients had some baseline CKD (as evidenced on biopsy) which makes them more vulnerable to AKI. Patient D had mesangial IgA deposits in the kidney which may be

mean he had pre-existing IgA nephropathy (IgAN) or it was an incidental IgA deposition. However, the kidney biopsy findings in patient D were not suggestive of IgAN. Both patients improved after stopping the formulation and with the addition of a short course of low dose steroids.

A multi-pronged approach for prevention includes increased awareness for both providers and patients of the potential nephrotoxicity of herbal formulations. A high index of suspicion of potential toxicity is necessary for early recognition and management.

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