www.nephropathol.com DOI: 10.15171/jnp.2018.59 J Nephropathol. 2018;7(4):296-300

Journal of Nephropathology

A case series on *Averrhoa bilimbi* induced acute oxalate nephropathy; an experience from a tertiary center in Kerala, India

Zuhara Shemin Kooloth Mahamoodh[1*], Seethalekshmy Nalumackal Vijayan[2], Annie Jojo[2]

[1]Department of Pathology, MES Medical College, Kerala University of Health Sciences, Perinthalmanna, Kerala, India
[2]Department of Pathology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India

ARTICLE INFO

Article type:
Case Series

Article history:
Received: 8 February 2018
Accepted: 28 April 2018
Published online: 19 May 2018

Keywords:
Acute oxalate nephropathy
Irumban Puli
Averrhoa bilimbi

ABSTRACT

Background: *Averrhoa bilimbi* is a commonly used fruit in South India for various home preparations and as a traditional remedy for hypercholesterolemia and hypertension. As it belongs to Oxalidaceae family, fruit has high oxalate content, causing calcium oxalate crystal deposition in renal tubules, resulting in acute oxalate nephropathy (AON) when consumed in large quantities.

Case Series: We present a series of 24 patients from 11 hospitals in the State of Kerala who developed acute renal failure after some days of intake of *Irumban puli* fruit juice. Seven patients needed hemodialysis while the other three improved with conservative management.

Conclusions: We conclude that it is not safe to consume high oxalate containing fruits, especially in concentrated forms, that too in large quantities.

Case Series

Implication for health policy/practice/research/medical education:
Irumban Puli (*Averrhoa bilimbi*) is commonly used as an ingredient of various South Indian dishes. It is also used in various other South East Asian countries for the indigenous method of treatment of diseases like hypertension, diabetes and hypercholesterolemia. Consumption of highly concentrated fruit juice can lead to acute renal failure due to acute tubular necrosis. The high oxalate content leads to Intra-tubular oxalate crystal deposition and renal failure. Hence, we conclude that it is not safe to consume such fruits with high oxalate content, especially in concentrated forms.

Please cite this paper as: Mahamoodh ZSK, Nalumackal Vijayan S, Jojo A. A case series on Averrhoa bilimbi induced acute oxalate nephropathy; an experience from a tertiary center in Kerala, India. J Nephropathol. 2018;7(4):296-300. DOI: 10.15171/jnp.2018.59.

1. Background

Secondary oxalosis can be due to increased ingestion, increased production, or decreased excretion of oxalate, leading to excessive oxalate accumulation and subsequent oxalate nephropathy. As oxalate has urinary excretion, increased oxalate load can lead to renal insufficiency (1,2). Case reports describing excessive intake of star fruit (*Averrhoa carambola*) juice (3,4) and peanut intake (5) leading to oxalate nephropathy are available. *Irumban puli* (*Averrhoa bilimbi*), belonging to the same genus as *A. carambola*, also has high oxalic acid content. It has commonly seen in South India and is used in various preparations. Excessive ingestion of fruit juice results in increased serum oxalate level. Calcium oxalate crystals are deposited in renal tubules and finally results in acute renal failure. We present a series of 24 cases from 11 different hospitals in the state of Kerala, during the study period 2010-2013, who developed acute oxalate nephropathy (AON) after consumption of *I. puli* juice.

2. Materials and Methods

We conducted a retrospective study on 24 patients from 11 different hospitals in Kerala, whose renal biopsies were sent to our laboratory for histopathological examination. We analyzed the following parameters; Age, gender, symptoms, comorbidities, blood pressure, ultrasonography findings of kidney, urine analysis with microscopic examination, serum creatinine levels,

*Corresponding author: Zuhara Shemin, Email: zuharasalman@gmail.com

quantity of fruit juice consumed, time for recovery and detailed histology along with the follow up. The details of the cases are illustrated in Tables 1, 2 and 3.

3. Results

Majority of the cases were males (M: F = 7:1) and belonged to the age group of 40-60 years. However, there were cases as young as 25 years to as old as 75 years. All of them had consumed the *A. bilimbi* juice as a traditional remedy for either hypertension or dyslipidemia except for a group of 3-4 youngsters, who had consumed wine prepared using the same fruit. Regarding the comorbidities, 8 patients had hypertension, two had diabetes mellitus, one had hypertension and diabetes mellitus, one had dyslipidemia along with hypertension and two had dyslipidemia only. Rest of the patients were devoid of any comorbidities.

Oliguria and edema were seen only in minority of cases. This variation could be due to lack of data received from referring hospitals. Majority had urinary oxalate crystals (16/24 cases). Serum creatinine values varied from 2.4–14.5 mg/dL. Around 19 patients had creatinine more than 5 mg/dL. Moreover, 58% cases underwent hemodialysis and renal biopsy, while 42% were treated conservatively. All of the 15 cases with renal biopsy showed features of AON. The photomicrographs of a representative case are given in Figure 1.

Ultrasonographic findings were normal in all the cases except for changes due to comorbidities like presence of diabetes, in respective patients. The proportion of fruits consumed varied from 20-100 mL/d. Majority had consumed it as concentrated juice 100-400 mL/d, either as single dose or as multiple doses, as a traditional remedy for their comorbidities, mostly on empty stomach.

4. Follow up of case series

All 15 patients who had hemodialysis recovered soon within few days. Creatinine levels normalized within 6-8 weeks. All those who were managed conservatively also recovered.

5. Discussion

Oxalate nephropathy can be of two types as primary hyperoxaluria and secondary hyperoxaluria. Primary

Table 1. Clinical and Demographic details of patients

Parameters	Cases								
	1	2	3	4	5	6	7	8	9
Age/gender (y)	38/M	57/M	35/M	49/F	53/M	65/M	45/M	56/M	72/M
Comorbidities	-	DM	-	HTN	-	-	HTN	-	HTN
BP (mm Hg)	150/90	150/90	180/100	-	120/80	108/78	128/84	116/80	130/80
Edema	-	-	-	-	-	-	-	+	-
Oliguria	-	+	-	+	-	-	+	-	+
Urinary oxalate	++	++	?	?	-	++	++	+	+
Highest serum creatinine (mg/dL)	6.4	9.3	11.2	5.5	12.3	6.7	9.8	6.6	5.2
Hemodialysis done/not	Y	Y	Y	Y	Y	N	Y	Y	Y
Kidney biopsy	Y	Y	Y	Y	Y	N	Y	Y	Y

HTN; hypertension, BP; blood pressure, DM; diabetes mellitus, Y; yes, N; no.

Table 2. Clinical and Demographic details of patients

Parameters	Cases								
	10	11	12	13	14	15	16	17	18
Age/gender (y)	46/M	40/M	29/M	33/M	50/M	28/M	55/M	42/F	75/M
Comorbidities	HTN	HTN	-	HTN	-	-	HTN	DM	DM,
BP (mm Hg)	140/90	140/80	140/80	170/110	170/100	150/100	130/80	130/80	-
Edema	-	-	+	?	+	-	-	+	-
Oliguria	-	+	+	+	-	-	-	-	-
Urinary oxalate	++	NA	NA	NA	NA	NA	++	++	++
Highest serum creatinine (mg/dL)	10.4	13	14.5	10	5.7	12	6	5.5	5.5
Hemodialysis done/not	Y	Y	Y	Y	Y	Y	N	N	N
Kidney biopsy	Y	Y	Y	Y	Y	Y	N	N	N

HTN; hypertension, BP; blood pressure, DM; diabetes mellitus, Y; yes, N; no.

Table 3. Clinical and demographic details of patients (continued).

Parameters	Cases					
	19	20	21	22	23	24
Age/gender (y)	35/M	25/M	57/M	70/M	53/F	45/M
Comorbidities	-	-	HTN/DLP	DLP	HTN	DLP
BP	-	-	130/80	130/80	150/90	140/90
Edema	-	-	-	+	+	-
Oliguria	-	-	-	-	-	-
Urinary oxalate	++	++	++	++	++	++
Highest serum creatinine (mg/dL)	7.5	3	3.5	2.4	4.9	5
Hemodialysis done/not	N	N	N	N	N	N
Kidney biopsy	N	N	N	N	Y	N

HTN; hypertension, BP; blood pressure, DM; diabetes mellitus, Y; yes, N; no.

hyperoxaluria is an autosomal recessively inherited enzyme deficiency disorder that leads to the increased urinary excretion of oxalate. There is a reduction of alanine-glyoxylate transaminase (AGT) activity in liver, leading to the accumulation of oxalate (1), in type 1 primary hyperoxaluria. While, type 2 primary hyperoxaluria occurs due to a mutation of glyoxylate reductase/D-glycerate dehydrogenase, resulting in increased excretion of L-glyceric acid as well as oxalate (2).

The causes for secondary hyperoxaluria are increased dietary oxalate intake, enteric hyperoxaluria and increased production of oxalate. Enteric hyperoxaluria usually results from fat malabsorption. Enteric hyperoxaluria occurs in orlistat therapy (6,7), Roux-en-Y gastric bypass surgery (8), celiac disease, and Crohn's disease. Increased production of oxalate is mainly due to glyoxylate accumulation, which is associated with ethylene glycol ingestion (9), and less commonly ascorbic acid (10).

Deposition of calcium oxalate crystals within the renal tubules results in acute renal failure in AON. *Averrhoa bilimbi* (commonly known as *bilimbi*, *Irumban puli*, *Chemmeen Puli*, *bimbul*) is a fruit-bearing tree of the genus *Averrhoa*, family *Oxalidaceae*. *Bilimbi* tree grows 5-10 m in height (11). It is widely cultivated in the tropical countries. Fruits are produced in clusters, cylindrical with five broad rounded longitudinal lobes (Figure 2). *A. Bilimbi* fruits are very sour, and are used in the production of vinegar, wine, pickles, jams and jellies and in the preparation of South Indian dishes.

Averrhoa bilimbi is commonly used as a natural remedy for the treatment of hyperlipidemia, hypertension and diabetes (12) in different parts of India, especially the leaves, flowers and fruits. In rats, it has been shown that this fruit has a cholesterol lowering effect (13). The fruit is also used to treat tinea versicolor, mumps, rheumatism, beriberi, cough, and scurvy. The oxalate content of the fruit was found to be 25.1 mg/100 g of fruit when analyzed in our laboratory which is very high

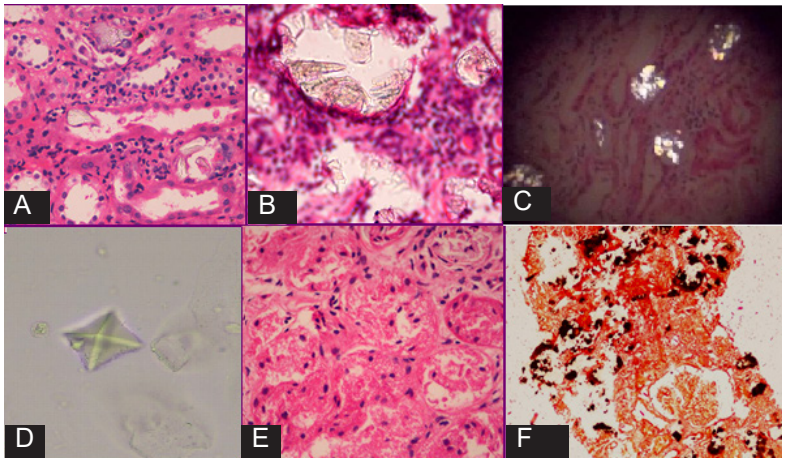

Figure 1. (A) Renal tubules showing features of acute tubular necrosis with fractured crystals in the lumen (LM-40x, H&E stain); (B) 100x, H&E stain ; (C) Calcium oxalate crystals under polarized light; (D) Urine microscopy showing calcium oxalate crystals (envelope shaped); (E) tubules with necrosis (40x, H&E stain); (F) demonstration of calcium oxalate with Von Kossa stain(black areas).

Figure 2. (A) *Averrhoa bilimbi* flower; (B) *Averrhoa bilimbi* fruit.

compared to other fruits (Table 4). The high levels of oxalic acid found in *bilimbi* are probably responsible for its extremely low pH (0.9-1.5).

Various renal and neurological side effects like muscle weakness, intractable hiccups, mental confusion, seizures can develop after ingestion of star fruit (*Averrhoa carambola*) (14,15). However, acute tubular necrosis due to *A. bilimbi*, ingestion is being reported for the first time. Oxalic acid damages the renal tubules and interstitium. Oxalate crystals get endocytosed by renal epithelial cells which damage renal epithelial cells and stimulate specific genes in renal tubular cells by the crystals, including the connective tissue growth factor gene, finally causing interstitial fibrosis.

All our patients had a history of intake of *Averrhoa bilimbi* juice. Calcium oxalate crystals detected in the urine of 8 patients. Intratubular polarizable crystals of oxalate were detected in 15 patients, with kidney biopsy.

6. Conclusions

Irumban puli (*Averrhoa bilimbi*) is commonly used as an ingredient of various South Indian dishes. It is also used in various other South East Asian countries for the indigenous method of treatment of diseases like hypertension, diabetes and hypercholesterolemia. Consumption of highly concentrated fruit juice can lead to acute renal failure due to acute tubular necrosis. The high oxalate content leads to intratubular oxalate crystal deposition and renal failure. Hence, we conclude that it is not safe to consume such fruits with high oxalate content, especially in concentrated forms.

Authors' contribution

SNV, AJ and ZS designed and performed the research. Zuhara Shemin and Seethalekshmy collected the histopathological data. ZS, SNV and AJ analyzed data and wrote the manuscript. All authors reviewed, edited and approved the final manuscript.

Acknowledgments

We acknowledge essays and efforts of nephrology staffs as follows; Anil Mathew (AIMS Kochi), P.M. Jayaraj (Mother Hospital Thrissur), Kishore Dharan (MOSC Medical College, Kolenchery), P.P. Jose (Lissie Hospital, EKM), Jaya Kumar, Department of Nephrology, (Govt. Medical College, Kottayam), R. Rajesh (St. Gregorius Medical Misssion Hospital, Parumala), Manju Thampi (NIMS, TVM), Geetha M (PRS hospital, TVM), Arun (Govt. Medical College, Trichur), Binu Upendran (Lourde's Hospital, Kochi), Jacob George (Govt. Medical College, TVM), T.T Paul(West fort hospital, TCR) and Kannan Vaidyanathan, Dept of Biochemistry, AIMS, Kochi. This paper has been presented as an oral paper for Indian Association of Pathologists and Microbiologists-Kerala Chapter Meet- 2013.

Table 4. Oxalate content of various fruits (16)

Fruits	Oxalate content (mg/100 g)
Cranberry	1.1
Grape	1.6
Tomato	5.5
Pineapple	7.3
Orange	2.2
Apple	0.5
Banana	3.2
Averrhoea Bilimbi(*Irumban Puli*)	25.1

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patients had given their informed consent regarding this case series report.

Funding/Support

There is no source of funding for this publication

References

1. Williams HE, Wandzilak TR. Oxalate synthesis, transport and the hyperoxaluric syndromes. J Urol. 1989; 141(3):742-7. doi: 10.1016/S0022-5347(17)40999-2.
2. Chlebeck PT, Milliner DS, Smith LH. Long-term prognosis in primary hyperoxaluria type II (L-glyceric aciduria). Am J Kidney Dis. 1994; 23(2):255-9.
3. Chen CL, Fang HC, Chou KJ, Wang JS, Chung HM. Acute oxalate nephropathy after ingestion of star fruit. Am J Kidney Dis. 2001; 37(2):418-22.
4. Nitiсharoenpong K, Chalermsanyakorn P, Panvichian R, Kitiyakara C. Acute deterioration of renal function induced by star fruit ingestion in a patient with chronic kidney disease. J Nephrol. 2006; 19(5):682-6.

5. Sasaki M, Murakami M, Matsuo K, Matsuo Y, Tanaka S, Ono T, et al. Oxalate nephropathy with a granulomatous lesion due to excessive intake of peanuts. 2008;12(4):305-308. doi: 10.1007/s10157-008-0046-5.
6. Karamadoukis L, Shivashankar GH, Ludeman L, Williams AJ. An unusual complication of treatment with orlistat. Clin Nephrol. 2009; 71(4):430-2.
7. Singh A, Sarkar SR, Gaber LW, Perazella MA. Acute oxalate nephropathy associated with orlistat, a gastrointestinal lipase inhibitor. Am J Kidney Dis. 2007; 49(1):153-7. doi:10.1053/j.ajkd.2006.10.004.
8. Nelson WK, Houghton SG, Milliner DS, Lieske JC, Sarr MG. Enteric hyperoxaluria, nephrolithiasis, and oxalate nephropathy: Potentially serious and unappreciated complications of Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2005; 1(5):481-5. doi:10.1016/j.soard.2005.07.002.
9. Stokes MB. Acute oxalate nephropathy due to ethylene glycol ingestion. Kidney Int. 2006; 69(2):203. doi: 10.1038/sj.ki5000107.
10. Nzerue C, Adelekun O, Rodriguez J, Sidani M, Chipman C. Oxalate nephropathy with AIN due to vitamin C intake. Am J Kidney Dis. 2009; 53:B58.
11. Janick J, Paull RE. The Encyclopedia of Fruit and Nuts. Wallingford: CABI Publishers;2008. p. 575.
12. Tan BK, Tan CH, Pushparaj PN. Anti-diabetic activity of the semi-purified fractions of Averrhoa bilimbi in high fat diet fed-streptozotocin-induced diabetic rats. Life Sci. 2005; 76(24):2827-39. doi: 10.1016/j.lfs.2004.10.051.
13. Ambili S, Subramoniam A, Nagarajan NS. Studies on the antihyperlipidemic properties of *Averrhoa bilimbi* fruit in rats. Planta Med. 2009; 75(1):55-8. doi: 10.1055/s-0028-1088361.
14. Neto MM, da Costa JA, Garcia-Cairasco N, Netto JC, Nakagawa B, Dantas M. Intoxication by star fruit (*Averrhoa carambola*) in 32 uraemic patients: Treatment and outcome. Nephrol Dial Transplant. 2003; 18(1):120-5.
15. Neto MM, Robl F, Netto JC. Intoxication by star fruit (*Averrhoa carambola*) in six dialysis patients? (Preliminary report). Nephrol Dial Transplant. 1998; 13(3):570-2.
16. Bakul G, Unni VN, Seethaleksmy NV, Mathew A, Rajesh R, Kurien G, et al. Acute oxalate nephropathy due to 'Averrhoa bilimbi' fruit juice ingestion. Indian J Nephrol. 2013;23(4):297–300. doi: 10.4103/0971-4065.114481.