Acute Kidney Injury with Neurological Features: Beware of the Star Fruit and its Caramboxin

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Abstract
Star fruit (Averrhoa carambola) is a well-known product in tropical countries. There are few reports published in literature with acute kidney injury due to oxalate induced nephropathy. However, none of them have an important neurological feature. We present a case of a 51-year-old male with paresis and altered mental status. Screening for neurological diseases such as stroke, Guillain-Barre, meningitis and encephalitis were negative. In the evolution, he developed acute kidney failure and was submitted to 4 dialysis sessions. After talking to the family, we discovered he had ingested over 50 star fruits prior to the acute neurologic deficits. He recovered renal function so a renal biopsy was not required. Physicians should actively look for star fruit ingestion history in patients presenting with unexplained acute kidney injury with or without neurological features. Besides, taking star fruit in a large amount, accompanied by an empty stomach and dehydrated state, is a risk factor for neurotoxicity.

Keywords: Acute kidney injury, Averrhoa, calcium oxalate, dialysis

Introduction
The star fruit (Averrhoa carambola), a member of Oxalidaceae family, is popular in tropical countries as Brazil, Mexico, and India. It is a star-shaped fruit that can be classified into two categories: the sour type—richly flavored, commonly prepared as juice and with more oxalic acid; and the sweet type—mild flavored, usually consumed as fresh fruit and with less oxalic acid.[1]

It is well known the toxicity of this fruit in chronic kidney disease. If ingested, patients with renal failure can have seizures, hiccups, mental confusion, coma and even death.[2]

Formerly it was believed that patient with normal renal function could ingest the fruit without any problems. However, isolated cases in literature proved that massive ingestion of this fruit can lead to acute kidney injury and neurotoxic effects. The first one caused by the amount of oxalate and the second due to caramboxin, the neurotoxin present in the star fruit that has renal excretion.[3]

The aim of this article is to report a patient who had an acute kidney injury with neurological deficits after consuming a large number of star fruits and to perform a literature review about the same.

Case Report
A 51-year-old man presented to the Emergency Department with paresis in right side and altered consciousness. He was previously healthy and denied drug use. No alcohol or tobacco history. His vital signs were normal, afebrile, no other abnormalities in the physical examination. A computed tomography (CT) was promptly performed for stroke evaluation. Admission CT was normal, with no signs of bleeding. We did not thrombolise the patient because he was no longer in the open window opportunity. Table 1 has other laboratory findings on admission.

At day 3 of hospitalization, he developed anuria, was tetraparetic and his creatinine value increased to 3.9 mg/dL. Another CT was performed that continued showing no acute ischemic insults. At this point, still believing in neurologic disease, the patient was submitted to lumbar puncture and magnetic resonance imaging, both without pathological findings. Herpes, Epstein-Barr, cytomegalovirus, VDRL serology, and real-time PCR for Mycobacterium tuberculosis were all negative. Even

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electromyography was performed to investigate Guillain-Barre or a myopathic disease, but it was negative as well.

Despite no signs of infection, we collected blood, urine and tracheal cultures that were all negatives. A urine exam showed more than 1 million leucocytes, 60 000 red cells, hyaline and granulose cylinders, and a 944 mg/dL protein. After this result, ceftriaxone was initiated empirically for urinary infection.

During the first week of hospitalisation he had to be dialysed four times due to hypervolemia. After dialysis initialization, we observed an improvement in his neurological deficits. A urinary ultrasound was unremarkable.

In his second hospitalization week, after a meticulous conversation with family, we discovered that he had ingested over 50 star fruits two-three days before presenting with paresis. After searching in literature, our hypothesis was that he had an acute kidney injury and neurological signs because of caramboxin intoxication. We did collect 24 h urine oxalate in the third week but it was within normal range (2.8 mg/24 h). That is probably because of the delay in sample collection (by that time he was having good urine output and renal functions were improving). A renal biopsy was not performed since the patient was having improvement. After one month the patient was discharged with no neurological deficits. His creatinine level was 1.3 mg/dL and urea 97 mg/dL. Six months after the initial event, in the nephrology outpatient clinic, his creatinine level was 1.3 mg/dL and urea 56 mg/dL.

For publication porpoise, the patient provided an informed written consent.

**Discussion**

There are few reported cases in the literature of star fruit toxicity [Table 2]. Notice that time since fruit ingestion and clinical presentation is highly variable, as so the amount ingested. From the published articles it can be concluded that if the patient has an empty stomach he does not need to consume a large amount of the fruit to develop the toxicity. On the other hand, a massive quantity (just like our case with 50 star fruits), independent of fasting, is a risk factor for neuro and nephrotoxicity.\[2\] We do not know, however, the precise maximum recommended amount of fruit or juice beyond which toxicity would be likely to appear.

Star fruit is a high source of oxalate. That explains the gastrointestinal symptoms that patients usually complain. They were not due to uremia as uremic symptom cannot develop soon after ingestion and suggest direct corrosive injury of oxalate in the digestive tract.\[4\]

The nephropathy induced by oxalate occurs a few hours later. The mechanism by which tubular damage occurred is the obstruction of renal tubules by these crystals as well as apoptosis of the renal tubular epithelial cells.\[5\]

The nephrotoxicity is strictly related to neurotoxicity. Star fruit has a neurotoxin called caramboxin, which has renal excretion and can pass through the blood-brain barrier. When renal function is abnormal there is an elevation of caramboxin in the central nervous system that results in neurological symptoms such as hiccups, paresis, seizure, coma and even death.\[2,6\] Moreover, there is no assay for caramboxin level yet available.

Neto et al.\[7\] had classified clinical symptoms of intoxication in uremic patients as 1) mild: hiccups (94%), vomiting (69%), and insomnia; 2) moderate: psychomotor agitation (66%), sudden-onset limb numbness, paresthesias (tingling/pricking) (41%), and muscle weakness; and 3) severe: moderate to severe mental confusion progressing to coma, seizures (22%) progressing to status epilepticus, and hemodynamic instability progressing to hypotension and shock.\[7,8\]

The treatment depends on clinical presentation, varying from conservative to dialysis. Some case reports used prednisolone in low doses, urinary alkalization, and diuretic therapy, all without a good evidence level.\[13\] Dialysis, on the contrary, seems the most reasonable treatment especially when neurological symptoms are present, since it is believed that caramboxin is dialyzable and may increase oxalate clearance, apart from the removal of uremic toxins.\[2,10\] However, there are no studies describing the use of hemodialysis for the sake of removal of oxalate per se without any other nephrological indications. We think that earlier dialysis can be performed if star fruit intoxication is hypothesized, especially with a disturbance in the conscious level or other neurological feature (peritoneal dialysis has been shown to be of no benefit, especially in these type of patients).\[10,13,14\] In our case, after initiation of dialysis sessions patients paresis improved. Dialysis could be started

**Table 1: Laboratory test exams at admission**

| Admission laboratory test                  | Result         |
|-------------------------------------------|----------------|
| Haemoglobin                               | 14.1 g/dL      |
| White blood cells                         | 8490/uL        |
| Platelet                                  | 264 000/uL     |
| Glucose                                   | 102 mg/dL      |
| Total bilirubin                           | 0,3 mg/dL      |
| Alanine transaminase                      | 66 U/L         |
| Aspartate transaminase                    | 80 U/L         |
| HIV, B and C hepatitis, VDRL               | Negative       |
| Urea                                      | 183 mg/dL      |
| Creatinine                                | 3.12 mg/dL     |
| Sodium                                    | 150 mmol/L     |
| Potassium                                 | 3.68 mmol/L    |
| Lactate                                   | 1.3 mmol/L     |
| Blood, urine, tracheal cultures           | Negative       |
| Lactate dehydrogenase                     | 403 ng/dL      |

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| Author and year | Patient details | Clinical manifestation and time after star fruit ingestion | Basal creatinine | Time for complete renal recovery and creatinine value | Histopathology | Urinary analysis | Dialysis | Comment |
|----------------|----------------|--------------------------------------------------|-----------------|-----------------------------------------------------|----------------|----------------|---------|---------|
| Present case   | Male, 51 years | 50 star fruits | Acute renal failure and paresis; 2-3 day | Not reported; 3.12 mg/dL at admission | 6 months; 1.3 mg/dL | Not performed | Leukocyturia, proteinuria and hematuria | Yes, 4 sessions | First report with a remarkable neurological finding |
| Molina et al., 2016 | Female, 55 year | 2-3 glasses in fasting bottle | Bilateral lumbar pain, nausea, asthenia; 2 h | Not informed; 4.55 mg/dL at admission | 3 weeks; 1.4 mg/dL | Not performed | Urate crystals | No | Treated with urinary alkalization with potassium citrate |
| Su et al., 2011 | Female, 63 years | 1000 mL of pure fruit juice on an empty stomach | Oliguria and leg edema; 5 days | Not informed; 6 mg/dL at admission | 1 month; 0.9 mg/dL | Oxalate nephropathy | Proteinuria and hematuria | No | - |
| Chen et al., 2001 | Male, 77 years | 1600 mL of pure sour juice on empty stomach | Nausea, vomiting, lower back pain; within hours | Not informed; 51 mg/dL four days after star fruit ingestion | 28 days; 1.5 mg/dL | Oxalate nephropathy | Hematuria | Yes, 2 sessions | First case report published |
| Male, 38 years | 3,000 mL of undiluted sour carambola juice on empty stomach | Abdominal pain and backache; 4 hours | Not informed, 1.6 mg/dL at admission | 28 days; 1.5 mg/dL | Oxalate nephropathy and IgA deposition in the mesangium | Not performed | Hematuria, proteinuria and leukocyturia | Yes, 5 sessions | Report with most precocious renal recovery |
| Scaranello et al., 2014 | Female, 44 years | Juice with 20 carambolas and ingested more 30 fruits | Diarrhea, nausea, vomiting, oliguria and abdominal pain; 1 day | 0.8 mg/dL; 9 mg/dL at admission | 10 days; 1.1 mg/dL | Not performed | Hematuria, proteinuria, leukocyturia and oxalate crystals | Yes, 2 sessions | - |
| Neto et al., 2009 | Male, 48 years | 15 fruits on empty stomach | Hiccups; 7 h | 0.89 mg/dL | Not informed; 1.1 mg/dL | Not performed | Not available | No | - |
| Male, 49 years | 1000 mL of pure juice | Hiccups, vomiting, insomnia; 3 h | 0.9 mg/dL; peak during hospitalization 6.2 mg/dL | Not informed; 1.1 mg/dL | Not performed | Hematuria | No | - |
| Female, 67 years | 1500 mL of pure juice | Hiccups, vomiting, diarrhea, back pain, mental confusion; 3 h | 1.2 mg/dL; peak during hospitalization 6 mg/dL | Not informed; 1.2 mg/dL | Not performed | Leukocyturia and oxalate crystals | No | - |
| Male, 66 years | 300 mL of pure juice, empty stomach | Hiccups, vomiting, back pain; half hour | 1 mg/dL; peak during hospitalization 5.6 mg/dL | Not informed; 1 mg/dL | Oxalate nephropathy | Oxalate crystals | No | - |
| Male, 34 years | 12 fruits, empty stomach | Back pain, nausea, insomnia; 1 h | 1.1 mg/dL; peak during hospitalization 4 mg/dL | Not informed; 1.1 mg/dL | Oxalate nephropathy | Oxalate crystals | No | - |
| Abeysekera et al., 2015 | Female, 56 years | 200 mL of concentrated juice of six star fruits | Generalized weakness and lethargy; 12 days | 0.9 mg/dL; 3.28 mg/dL at admission | 3 weeks; 0.96 mg/dL | Oxalate nephropathy | Proteinuria and leukocyturia | No | Given oral prednisolone due to the presence of interstitial nephritis |

Contd...
| Author and year | Patient Details of fruit ingestion | Clinical manifestation and time after star fruit ingestion | Basal creatinine | Time for complete renal recovery and creatinine value | Histopathology | Urinary analysis | Dialysis | Comment |
|----------------|-----------------------------------|----------------------------------------------------------|-----------------|-------------------------------------------------|----------------|-----------------|---------|---------|
| Barman et al., 2016 | Male, 30 years, 10 fruits, 500 mL juice, empty stomach | Abdominal pain, oliguria; 6-10 h | Not informed; 23.7 mg/dL at admission | Not informed | Acute tubular necrosis | Proteinuria and hematuria | Yes, number not available | Case series with more young patients |
| | Male, 29 years, 1000 mL juice | Abdominal pain, oliguria; 12-15 h | Not informed; 17.1 mg/dL at admission | Not informed | Acute tubular necrosis and oxalate nephropathy | Proteinuria | Yes, number not available | |
| | Male, 45 years, 5-6 fruits, 500 mL juice | Back pain, nausea, oliguria; 10-12 h | Not informed; 6 mg/dL at admission | Not informed | Acute tubular necrosis and oxalate nephropathy | Proteinuria | No | |
| | Male, 20 years, 6-8 fruits, empty stomach | Nausea, oliguria; 10-14 h | Not informed; 11.7 mg/dL at admission | Not informed | Acute tubular necrosis | Proteinuria | Yes, number not available | |
| Wijayaratne et al., 2017 | Female, 4-6 fruits | Hiccups, abdominal pain; 28-30 h | Not informed; 3.2 mg/dL at admission | Not performed | Oxalate nephropathy | Nothing remarkable | Yes, 1 session | - |
| | Male, 52 years, 200 mL of homemade star fruit juice made from four whole star fruits | Loose stool, abdominal pain, oliguria; few hours | Not informed; 0.7 mg/dL; 4.5 mg/dL at admission | 3 months; not informed | Oxalate nephropathy | Nothing remarkable | No | Given prednisolone 30 mg daily |
| | Male, 65 years, 3 star fruits | Poor appetite, poor sleep, nausea and dyspeptic symptoms; not informed | 1.2 mg/dL; 7.3 mg/dL at admission | 10 months; 1.4 mg/dL | Acute tubule-interstitial nephritis | Nothing remarkable | No | |
| | Male, 57 years, One star fruit daily over the preceding one year with increased consumption to 3 fruits per day over the preceding one month | Loss of appetite, nausea, diarrhea; consuming daily 3 fruits for the past month | Not informed; 13.16 mg/dL at admission | 2 months; 2.98 mg/dL | Oxalate nephropathy occurring in the background of early diabetic nephropathy | Hematuria and leukocyturia | Yes, number not informed | Given prednisolone 30 mg daily |
sooner even without classic indications due to severe neurological impairment, but star fruit intoxication was not one of our firsts differentials diagnosis.

Recently the effect of N-acetylcysteine on star fruit induced acute kidney injury was studied in animal models. The results suggest that this drug can reduce oxidative stress, oxaluria, and inflammation, attenuating renal dysfunction in the final analysis.[1] It is important to emphasize that acute events related to star fruit intoxication have a good prognosis. Every case reported in the literature had a recovery in renal function and no deaths. In chronic kidney disease, however, death can occur in 61% and 42% of patients with seizure and confusion, respectively.[2]

**Conclusion**

To the best of author’s knowledge, there is no report in literature with such important neurological feature in acute star fruit intoxication. Our diagnosis was delayed because we believed in neurological disease. The decrease in renal function helped to seek of other differentials, but the strong epidemiology of star fruit consume closed the diagnosis and no biopsy was needed. Therefore, every patient presenting with acute kidney failure with or without neurological features should be questioned about star fruit consume. Physicians should guide patients not to ingest a large amount of star fruit, especially on an empty stomach or in a dehydrated state.

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**Conflicts of interest**

There are no conflicts of interest.

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