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Teaching Point
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Star fruit: simultaneous neurotoxic and nephrotoxic effects in people with previously normal renal function

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Introduction

Patients with renal failure not yet on dialysis (stages 3–5) or on dialysis treatment are susceptible to intoxication from eating star fruit (Figure 1). In these patients, star fruit may cause mild to severe neurotoxicity including hiccups, vomiting, asthenia, mental confusion, seizures, coma and death [1–3]. However, there are anecdotal reports of individuals with normal renal function who became intoxicated as a result of eating or drinking a large amount of star fruit, and intractable and persistent hiccups are usually the main symptom.

Star fruit nephrotoxicity in people with normal renal function is rarely reported and it is never associated with signs of neurotoxicity. There is only prior one study of such cases, which reported on two cases of acute renal failure (ARF) due to acute oxalate nephropathy in patients with previous normal renal function [4]. In the current study, we present five patients with previously normal renal function who became intoxicated from eating star fruit or drinking star fruit juice and presented simultaneously nephrotoxic and neurotoxic effects.

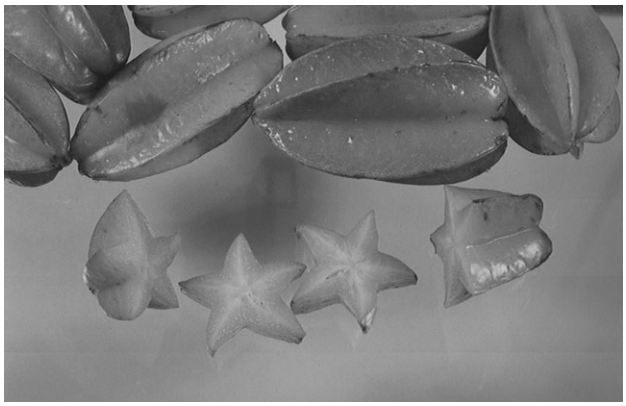

Fig. 1. Star fruit (*Averrhoa carambola*) or carambola has been cultivated in Malaysia, Southern China, Taiwan, India and Brazil. It is rather popular in the Philippines and Queensland, Australia and moderately so in some of the South Pacific Islands, particularly Tahiti, New Caledonia and Netherlands New Guinea, Guam and in Hawaii and south Florida. There are some subspecies in the Caribbean Islands, in Central America and in tropical West Africa. The fruits are also available in many European countries and Canada. Range of soluble oxalate salts concentrations obtained from many cultivars varies from 80 to 730 mg/100 g of the fruit [7].

Cases

We identified five patients with clinical or histological evidence of ARF associated with star fruit ingestion. The patients were analysed according to clinical features, the amount of ingested fruit and their renal function outcomes. Serum creatinine levels were used to characterize renal function. The initial median serum creatinine was 97.2 μmol/L. Four patients ingested a large amount of star fruit and one ingested 300 mL of pure star fruit juice on an empty stomach. The symptoms started 3–8 h after ingestion; four had acute renal failure, which was associated with back pain in three of the cases; four patients displayed simultaneous neurotoxic (intractable hiccups, vomiting and insomnia) and nephrotoxic effects, and one presented with only neurotoxic effects (intractable hiccups). Their clinical presentation, sex, age, the amount of ingested fruit, previous serum creatinine levels, maximum levels of creatinine and outcomes are summarized in Table 1. Renal biopsies performed on patients 4 and 5 (Figure 2) indicated a typical histological appearance of acute tubular necrosis

Table 1. Clinical features of patients who ingested star fruit

Patient	1	2	3	4	5
Age (years)	48	49	67	66	34
Sex	Male	Male	Female	Male	Male
Amount of ingested fruit	15 fruits	1000 mL of pure juice	1500 mL of pure juice	300 mL of pure juice	12 fruits
Time length used to ingest the fruits or juice (hours)	7	3	3	Half hour	1
Ingestion of food	Empty stomach	Light meal	After lunch	Empty stomach	Empty stomach
Symptoms	Hiccups	Hiccups; vomiting; insomnia	Hiccups; vomiting; diarrhoea; back pain; mental confusion	Hiccups; vomiting; back pain	Back pain; nausea; insomnia
Urinary sediment	N/A	6 leukocytes and 13 red cells per high power field	480 000 leukocytes/mL culture negative and free of oxalate crystals	4–6 leukocytes per high power field and free of oxalate crystals	5–6 leukocytes per high power field and free of oxalate crystals
Previous serum creatinine μmol/L	79.5	88.4	106.2	88.4	97.2
Peak of creatinine μmol/L	N/A	548.0	530.4	495.0	353.6
Creatinine after acute episode μmol/L	97.2	97.2	106.2	88.4	97.2
Kidney biopsy	No	No	No	Oxalate nephropathy	Oxalate nephropathy

N/A: not available.

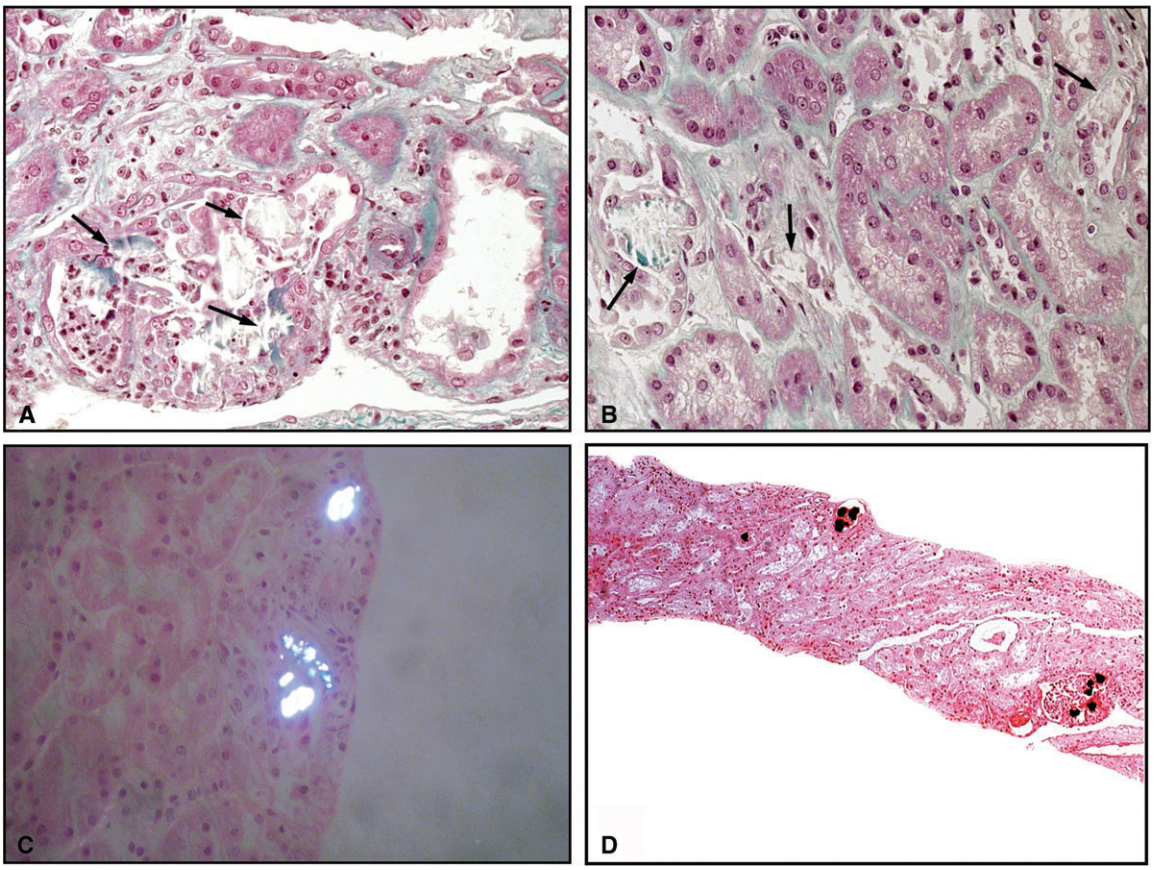

Fig. 2. Microscopic views of biopsy specimens from cases 4 (**A** and **D**) and 5 (**B** and **C**). Light microscopy showing oxalate crystals (arrows) within the lumina and tubular walls surrounded by inflammatory infiltration (Masson's Trichrome, original magnification × 40) (**A** and **B**). Renal section analysed under polarized light showing several colourless oxalate crystals with a pattern of birefringence within the tubular lumina (Haematoxylin and eosin, original magnification × 10) (**C**). Renal section stained after von Kossa stain (**D**) displaying oxalate crystals with a typical black colour (original magnification × 10).

and oxalate nephropathy. In both cases, light microscopy (A and B) showed oxalate crystals (arrows) within the lumina and tubular walls surrounded by inflammatory infiltration that included lymphocytes, histiocytes and primarily neutrophils. Tubular focal dilation, desquamated cells in the lumina, lining cell flattening and interstitial oedema were also present. Renal sections were analysed under polarized light and showed colourless oxalate crystals with a pattern of birefringence within the tubular lumina (C). The oxalate crystals displayed a typical black colour after Von Kossa staining (D). It is noteworthy that none of the patients were given dialysis. The median serum creatinine after recovery was 97.2 μmol/L.

Discussion

The first patient presented hiccups and no laboratory tests were performed. Two other patients (numbers 2 and 3) showed acute renal failure and neurotoxic symptoms as persistent hiccups and mild mental confusion. Patients 4 and 5 had acute renal failure and were biopsied. The biopsies showed acute oxalate nephropathy. Patient 4 presented with hiccups as a neurotoxic symptom, and patient number 5 showed mild neurotoxicity (insomnia). In these reports, all patients had good outcomes without dialysis, in contrast with a previous report of two patients who were submitted to haemodialysis [4]. Following the first descriptions [1–3] of neurotoxicity in patients with chronic kidney disease (CKD) stages 3–5, many other instances of star fruit intoxication have been reported, which are described in an extensive review [5]. Neurological symptoms are common presentations of star fruit intoxication in patients with CKD stages 3–5, regardless of whether they are on dialysis, leading some patients to death due to severe intoxication as coma and status epilepticus refractory to conventional therapy [2–4]. Intensified and prompt treatment with intensified haemodialysis and haemoperfusion associated with aggressive supportive care, including ventilator and cardiovascular support have been proposed as effective initial therapies; however, star fruit toxicity may still be fatal [2,3,5,6].

Star fruit is also a high source of oxalate [4,7]. Chen *et al*. [4] described two cases of acute renal failure associated with acute oxalate nephropathy but did not report any neurotoxic symptoms. There are no other reports of star fruit intoxication in people with normal renal function, except for many anecdotal reports of hiccup episodes after ingestion of large amounts of the fruit. Normally these hiccups will cease spontaneously after a few hours, and no laboratory tests were performed in the majority of cases, as described in case 1.

Star fruit and other plants containing oxalates may present neurotoxic and nephrotoxic effects in humans and animals [8]. Fang *et al*. [9,10] showed that star fruit with abundant oxalate content could cause acute oxalate nephropathy in rats. According to these authors [10], acute kidney injury is provoked by oxalate not only through the obstructive effect of calcium oxalate crystals but also by inducing apoptosis of renal epithelial cells. In other experimental studies [11,12], the authors concluded that oxalate may play a key role in star fruit neurotoxicity in nephrectomized rats and probably in uraemic patients. In humans, the situation may be different because we do not know of any description of neurotoxic effects in uraemic patients after ingestion of foods rich in oxalate, such as spinach, rhubarb, tea, beets (leaves and sugar) and coconut [7]. Niticharoenpong *et al*. [13] described a patient with underlying chronic disease who had developed a rapid increase in serum creatinine and had oxalate nephropathy (as verified by kidney biopsy) after chronic ingestion of star fruit juice without overt neurotoxicity. One of the patients described here (case 5) had acute oxalate intoxication and displayed only mild neurotoxic symptoms (insomnia). In a previous report [14], a fraction purified from star fruit, but devoid of oxalate, still maintains its convulsant effects when applied to the rat brain. In fact, Garcia-Cairasco *et al*. [15] have shown that intrahipocampal applications of the star fruit pure toxin, which they have called caramboxin, act as convulsant and neurotoxic substance as well. These data suggest that caramboxin may be the most potent neurotoxic component present in star fruit. However, in the case of human intoxication in renal patients or in the individuals with normal renal function, an interaction of caramboxin and oxalate cannot be ruled out.

These cases of acute nephropathy induced by star fruit ingestion, along with those previously described in the literature [4,13], confirm the existence of this new disease and raise new speculations. One of these speculations is related to epidemiology area. We believe this form of acute nephropathy to be much more frequent than the few cases that have been reported. As more doctors become aware of the symptoms associated with star fruit ingestion, we may observe an increase in diagnosed cases.

We still do not know the maximum recommended amount of fruit or juice beyond which toxicity would be likely to appear. It is necessary to determine the minimum amount of ingested star fruit that can provoke acute oxalate nephropathy and whether there are individual risks that can increase the likelihood of nephropathy. The lethal dose of soluble oxalate for humans varies from 2 to 30 g [16] and soluble oxalate concentration in star fruit varies from 80 mg/100 mL to 730 mg/100 mL [7].

In individuals who present with simultaneous neurotoxic and nephrotoxic effects, we might consider the following sequence of events: ingestion of large amount of oxalate in star fruit causes acute oxalate nephropathy and acute renal failure, followed by neurotoxic effects (mostly hiccups) triggered by a putative star fruit neurotoxin (caramboxin) that accumulates in these patients due to renal failure and finishes as soon as renal function improves.

Large amounts of star fruit ingestion, or even smaller amounts on an empty stomach, may provoke simultaneous acute renal failure and neurotoxicity in people with previously normal renal function. Physicians should be warned that people with previously normal renal function who have ingested star fruit and present with one or more specific symptoms (intractable hiccups, back pain and/or mental confusion) should be screened for acute renal failure caused by acute oxalate nephropathy.

Teaching points

Star fruit is very prevalent in some tropical and subtropical areas in the world and its consumption is high especially in Asia and South and Central America. Therefore, star fruit toxicity in patients with CKD has mainly been reported from those areas.

- Nephrotoxicity and neurotoxicity provoked by the ingestion of the fruit or juice, sometimes fatal, is far more frequent than reported.
- Patients with CKD stages 3–5 not yet on dialysis and all patients on dialysis should be warned to avoid eating star fruit.
- Individuals with normal renal function should be warned to avoid ingestion of large amounts of the fruit or juice especially on an empty stomach.
- As we do not know whether all nephrologists caring for dialysis patients are aware that star fruit should be banned from the patients's diet, and whether there are any public health organizations caveats regarding star fruit toxicity, we recommend that this should be implemented.

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Conflict of interest statement. None declared.

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