
*Case report***A Rare Etiology among the Huge Burden of Herbal Nephrotoxicity**

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Abstract

Kidney is the target of many natural toxicants because of its rich vascularization and the major role in their metabolism and elimination. Herbs are believed to be "natural" and safe but they may have serious side effects such as nephrotoxicity. Eucalyptus is used as an antiseptic, expectorant, antibacterial remedy especially for asthma, bronchitis, sore throat and rhinosinusitis in varying forms. The main clinical side effects of eucalyptus preparations are epigastric pain, vomiting, symptoms from central nervous system (CNS), a burning sensation in the mouth/throat and respiratory distress. Nephrotoxicity due to eucalyptus exposure is very rarely reported in the literature.

Key words: eucalyptus; acute kidney injury; renal dialysis

Introduction

The kidney is very susceptible to toxicity. The use of herbs and herbal supplements has been increased among people as an alternative treatment in chronic diseases. The best known example of these remedies resulting in renal failure is Aristolochic acid-Chinese herbs nephropathy which may cause uroepithelial malignancies, renal interstitial fibrosis and tubular atrophy as well as Fanconi syndrome [1]. Traditionally, herbs have been considered to be non-toxic and harmless, because of their natural origin. However, they may contain contaminants, such as heavy metals and pesticides. Herein we report a rare case of herbal nephrotoxicity presenting with acute renal failure (ARF) requiring temporary hemodialysis that was probably due to eucalyptus tea. In cases of unexplained ARF, alternative/herbal medicine use should always be considered.

Case

A 61-year-old man with a 2-year history of hypertension treated by amlodipin 10 mg tb 1*1, valsartan/hydrochlorothiazide 160/12.5 mg tb 1*1 was admitted to the Department of Emergency Service. He suffered from fati-

gue and dizziness for five days. He had no history of renal failure, contrast media exposure or surgical intervention. The family history of the patient was not contributory. Blood pressure was 160/100 mm/Hg, heart rate 80/min, temperature 36.5° C. The rest of the physical examination was normal apart from bibasilar rhonci. Chest X-ray was normal without any pulmonary infiltration, nor enlarged cardiothoracic index. Blood tests showed the following: ESR: 99 mm/first hour, random blood sugar: 148 mg/dl, serum urea: 231 mg/dl, creatinine: 6.12 mg/dl, uric acid: 14.1 mg/dl, calcium: 10.2 mg/dl, potassium: 5.8 mmol/l, sodium: 124 mmol/l, phosphorus: 6.8 mg/dl, PTH: 129.8 pg/ml, albumin: 3.8 gr/dl, WBC 13400, hemoglobin: 11.3 g/dl, hematocrit: 32.7%, platelets: 250000 and CRP: 127.58 mg/dl. Urinalysis revealed specific gravity of urine sample of 1010 and pH: 5.



Fig. 1. Leaves of Eucalyptus spp.

No protein and leukocytes were found in the urine but some erythrocytes (3/high power field) were present whereas spot urine sodium was 20 mmol/l. A consultation from nephrologists was requested because of in-

creased urea and creatinine levels. Two months ago the patient had normal renal function (serum creatinine 0.8 mg/dl). As we deepened the medical history to better understand the cause of renal failure, we found out that he had been drinking eucalyptus tea (approximately 20-30 ml per day) for natural treatment of his hemorrhoids for the last 7 days (Figure 1).

Venous blood gas analysis showed metabolic acidosis; Ph 7.29, $p\text{CO}_2$ 48.1, HCO_3 22.7. Glomerular filtration rate was calculated as 10.21 ml/min/1.73 m² according to MDRD formula. Renal ultrasonography of the right kidney showed that right kidney was 102*56 mm with parenchymal thickness of 16 mm and normal echogenicity, with a focal ectatic area of 1.5 cm in the upper anterior pole. The left kidney was 105*57 mm with parenchymal thickness of 17 mm and normal echogenicity. There was no sign of stone on ultrasonography. A central catheter was placed and he was subjected to intermittent hemodialysis. Amlodipine 5 mg tb 1*1, sodium hydrogen carbonate 500 mg tb 3*1 and calcium polystyrene sulfonate 1*1, bronchodilator therapy were added to the medication. Daily urinary protein excretion was 196 mg/day and microalbuminuria 72 mg/day was detected in the twenty-four hour urine sample. Serum immunoglobulins and complement components were within normal limits. Antinuclear antibodies, AMA, ANCA, ASMA, Anti HCV Ab and hepatitis B surface antigen were also negative. The rest of the biochemical tests revealed transferrin saturation of Fe%: %27, ferritin 572.35 ng/ml, vitamin B12: 132 pg/ml, folate: 3.7 ng/ml, TSH: 1.19 mIU/ml, free T4: 1.42 ng/dl. The ECG was normal with sinus rhythm, without any pathological findings. After undergoing hemodialysis for 4 sessions, his urinary output remained satisfactory throughout. During the follow-up period without hemodialysis his urea and creatinine levels regressed to 107 mg/dl and 1.84 mg/dl, respectively. He was discharged from hospital. A renal biopsy was not planned at first step due to the rapid regression of urea and creatinine levels. During the close follow-up his laboratory findings stayed stable; after 2 months he was re-admitted to the hospital. Serum urea was 48 mg/dl and creatinine value 1.41 mg/dl. Arterial blood gas analysis was normal. Finally, after 5 months he had urea 36 mg/dl and serum creatinine 1.04 mg/dl. Since there was no evidence of potential etiology for acute renal failure, this might be possibly attributed to the exposure of eucalyptus.

Discussion

The market for the herbal remedies and natural products is growing rapidly worldwide. It has been documented that about 40% of Americans use dietary supplements [2]. In general, herbs are believed to be "natural" and safe but many dangerous and sometimes lethal side effects have been reported. This risk may be attributed to the contamination with pesticides and/or heavy metals

in the botanical product, and by minerals and/or prescription drugs in patent medicines. The high percentage of people who use herbal remedies do not mention this use to their physician or pharmacist. This paradigm has been well-shown [3]. Because of this, many herbal poisonings are not diagnosed or treated correctly in every day clinical practice. The interactions between herbal components and concurrent pharmacotherapy represent a cause of increasing risk of side-effects from the use of these remedies [4].

Kidney is particularly susceptible to the action of many natural toxicants because of its anatomic and physiologic features, rich vascularization and its major role in metabolism and elimination of toxicants. The clinical manifestations of toxic nephropathy may vary from a mild reduction of renal function, hematuria, proteinuria, and urolithiasis to a severe progressive toxicity even to end-stage renal disease.

The prototype nephrotoxic supplement that is used so frequently is Chinese herbs containing the nephrotoxin-aristolochic acid [5-7]. Chronic exposure to Aristolochia acid (AA) can be involved in the renal fibrosis as well as in urothelial cancer [8]. Nephrotoxicity is an important issue when selecting Chinese herbal formula for the treatment of chronic diseases. Some of the other well-known herbal supplements are Chaparral, Ephedra, Yellow oleander, Thunder god vine, Willow bark [9]. Also, some natural medicines may be associated with kidney stones or increased urine excretion of kidney stone precursors as Calcium, Sorrel, Wood sorrel [10]. Such agents may cause urothelial cancers, acute renal failure and chronic renal failure. Possible interactions between herbal and conventional medications must be considered [11]. Ginkgo, St. John's wort, Ginseng, Echinacea, Sawpalmetto, Kava are some of the examples for these dangerous interactions between herbs and drugs [12]. There are about 600 species of Eucalyptus worldwide. Of all of these species, Eucalyptus Globulus is the most widely cultivated in subtropical and Mediterranean regions. Eucalyptus is used as an antiseptic, expectorant, antibacterial remedy especially for asthma, bronchitis, sore throat, rhinosinusitis in varying forms such as oil, tea, mouthwash. The main clinical side-effects of eucalyptus preparations are reported as epigastric pain, vomiting and CNS symptoms. In addition, a burning sensation in the mouth/throat and respiratory distress represent other adverse reactions. Respiratory symptoms may include bronchospasm and tachypnoea, with dangerous respiratory depression following severe intoxication. Central nervous system involvement includes seizures, diminution or loss of reflexes, and depression of consciousness which may progress to coma. Convulsions are rare in the adult but may be prominent in the child. Death is usually the result of respiratory failure or convulsions. Nephrotoxicity due to eucalyptus exposure is rarely reported in the literature [13,14]. Associated with ingestion of large amounts of mouthwash; in-

cluding eucalyptol; anion-gap acidosis and renal failure has been shown at a fatal case [14]. Direct nephrotoxicity may follow the ingestion of large quantities [15]. Mechanisms of kidney injury may include direct nephrotoxicity, which may be augmented by underlying predisposing conditions such as dehydration, contamination, inappropriate use or preparation of a remedy, or interactions with other medications. Eucalyptus preparations are capable of hepatic microsomal induction hence it may affect the metabolism of other drugs and chemicals using the common pathway. Studies with human liver microsomes have characterized the hydroxylation of eucalyptol by CYP3A enzymes [16]. In severe poisoning, peritoneal dialysis or haemodialysis may be necessary [13]. In some of the case reports hemoperfusion has been recommended, but these reports are poorly substantiated [17]. Leaves of eucalyptus are reported to contain a high content of eucalyptol (cineol) together with terpineol, sesquiterpene, alcohols, aliphatic aldehydes, isoamyl alcohol, ethanol, terpenes and tannins [18]. Worth, *et al.* reported no renal side effects whereas cineole was used in a multicenter study [19]. However, it was shown in animal studies that the presence of tannic acid, present in high concentrations in eucalyptus, potentiated the nephrotoxic effect of cisplatin on rats [20]. The nephrotoxic content in eucalyptus has not been clearly defined yet. Although in the related references the lethal human dose for menthol, thymol, and eucalyptol is estimated at 50-500 mg/kg, there is still no exact information on adequate estimates of toxic dose levels for eucalyptol [21].

Conclusion

Eucalyptus poisoning is not so frequently seen in clinical practice, especially among adults. Thus, we have found interesting enough to present this case report. Healthcare professionals should ask their patients about the use of herbal products and consider the possibility of herb-drug interactions. We should keep in our mind that the possibility of interactions between herbal and synthetic drugs can be fatal.

Conflict of interest statement. None declared.

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