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Case Report

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Khella induced nephropathy: a case report and review of literature

Abstract

Khella (Ammi visnagais) was used in Ancient Egypt as a herbal remedy for renal colic. Khella contains group of coumarins, xanthotoxin, ammidin, furoquinoline alkaloids and, dihydroseselins with varying cytotoxic activity. The most common is Khellin and visnagin. Khellin was found to be a smooth muscle relaxant, induces diuresis, increases excretion of citrate and decreases the excretion of oxalate in urine, which improves nephrolithiasis and passage of ureteric stones. Synthetic derivatives of khellin include amiodarone, the anti-arrhythmic drug, and cromolyn, an anti-asthma drug. Khellin is not as safe as it seems to be. Its oral use is limited by its potential toxicity (eg, elevated liver enzymes, phototoxicity, dermatitis). In experimental animals, the median lethal dose (LD50) was 3.6 g/kg for intra-peritoneal administration and 10.1 g/kg for oral administration. In humans, nausea and vomiting were observed frequently in 29% and transaminitis in 7-14% of the patients. Other potential adverse reactions include dizziness, constipation, headache, itching, insomnia, photosensitivity and lack of appetite. We report for the first-time, acute kidney injury following use of khella in a CKD patient with a 5-fold increase in his serum creatinine level from 1.9 to 9.2 mg/dl. His renal biopsy revealed eosinophilic interstitial nephritis. He responded well to pulse methylprednisolone followed by short course of oral steroids. We believe this is the first case describing Khella nephropathy. Herbal nephropathy is not uncommon and herbal remedies are not as safe as it is believed. Accurate diagnosis and early management are the key in improving the renal outcome.

Keywords: khella, urinary stones, chronic kidney disease, diuretics

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Abbreviations: CHN, Chinese herbs nephropathy; AA, aristolochic acid; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ALT alanine aminotransferase; AST, aspartate aminotransferase

Introduction

Herbal nephropathy was first described in Brussels, Belgium, when a group of women with shared social activity were diagnosed with similar nephritis associated with rapidly progressive kidney failure. All the women shared the same experience of taking weight-loss herbs called Aritolochia fangchi which contains Aristolochia acid.[1] This nephritis was termed "Chinese herbs nephropathy" (CHN) due to the origin of the weight-loss supplement.[2] Another herbal nephropathy was first reported in the southeastern Europe and named Balkan nephropathy. It was found that Balkan nephropathy was similar to Chinese herbal nephropathy and resulted from aristolochic acid (AA) consumption. Balkan nephropathy was more toward the chronic side and slowly progressive than the nephritis that is seen in Chinese herbal nephropathy and that related to the low level of aristolochia exposure, due to contamination of wheat flour seeds by another plant of the birthwort family calledaristolochia clematitis.[3]The group of birthwort plants was widely utilized thousands of years ago in ancient Greek and Roman empires, and well-established and documented as an important medical herb in the ancient texts by the fifth century BC.[4] Birthworts appeared in India in Ayurvedic texts by 400 AD, and in China in the fifth century. It was a treatment formulti-task actions on kidney and urinary problems, snakebites, gout, considered to be an effective contraceptive and one of many ingredients used to create ointments. In the early first century, in the Roman empire, aristolochic acids was the most famous medical component frequently ingested to treat things such as asthma, hiccups, spasms and pains.[4]

Khella (Ammi visnaga) is another famous plant utilized as a folkloric herbal medicine in the Mediterranean since pharaohs in Ancient Egypt; like most of the herbal remedies, it is used to treat a variety of diseases including renal colic, kidney stones, coronary disease, bronchial asthma, psoriasis and vitiligo.[5] Khellin is a major constituent of the plant Ammi visnaga, also known as Bishop's Weed. The purified form is colorless, odorless, bitter-tasting needle-shaped crystals[6] and is classified as a gamma-pyrone, a furanochromone derivative. Due to its toxicity, in the early 20th century, efforts succeeded to shift to khellin analogs with lower toxicity and better efficacy. Many drugs were innovated from khella as amiodarone and recordil which are used in current medical practice.[7]

Case report

A 67-year-old male, had type 2 diabetes mellitus, hypertension, and chronic kidney disease (CKD) stage 3 with estimated glomerular filtration rate (eGFR) 35.7 ml/min and, serum creatinine of1.9 mg/dl. He presented to the emergency room with shortness of breath, tachypnea, metabolic acidosis, uremic manifestations, high serum creatinine of6.5 mg/dlL which rose to 9.2 mg/dl in two days, with still having a satisfactory urine output of more than 2 liters per day. He gave history of taking herbal medicine 7-10 days earlier; he was drinking a bottle of boiledkhella seeds every day seeking to improve his kidney function. Autoimmune profile including anti-neutrophilic antibodies, anti-ds DNA, -, and anti-GBM were negative. Correction of metabolic acidosis with intravenous and oral sodium bicarbonate was performed (Figure 1). Renal biopsy was performed and empirical

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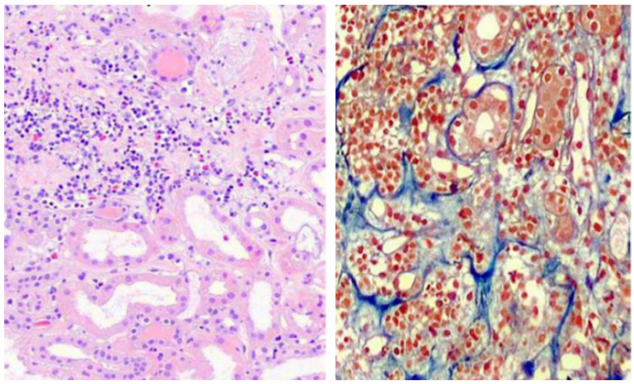
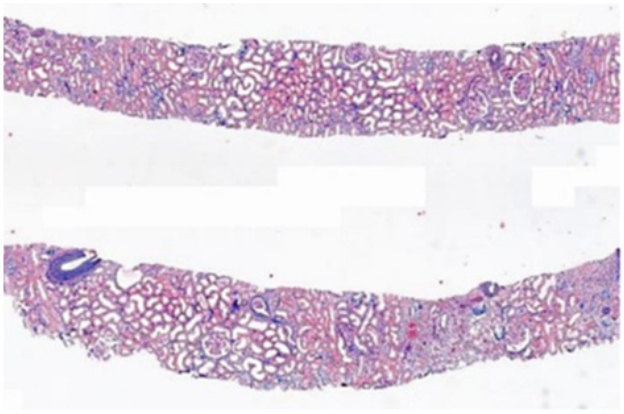
pulse methylprednisolone 500 mg for 5 days was initiated. Renal biopsy revealed tubulointerstitial nephritis with infiltration of eosinophils, acute tubular injury with calcification, mild chronic renal parenchymatous damage, arteriosclerosis, glomerulosclerosis of 15% and IFTA of 10% Figure 1(A,B). His kidney function partially improved with drop of serum creatinine to 7.5 mg/dl after completing steroids course. After couple of weeks and complete weaning of steroids, his serum creatinine returned back to basal 1.64 mg/dl Figure 1(C).



(A) Tubulointerstitial nephritis with Eosinophils & calcification, (B) Acute tubular injury



(C) Interstitial fibrosis

Figure 1 Renal Biopsy Histological Features of Khella Nephropathy

Discussion

Unfortunately, with the great innovations in the field of synthetic medications, there is still great reliance on the curative properties of plants. Herbal medicines are utilized by humans for general health and specific diseases since ancient times and are complex,based on various plants including weeds.[8,9] According to world health organization, majority (80%) of the inhabitants of rural areas depend on herbal medicine in their healthcare in developing countries.[10] An estimate of thousands of plant species are widely used for medicinal purposes worldwide.[11,12] Special attentionis required since the active ingredients derived from herbs have its own dose and toxicity as in conventional drugs,and this contributes to the conceivable harmful side effects.[13,14] Khella plant (Ammi visnaga) wasdiscoveredinancient times and acquired different names according to its geographical distribution.Ammi visnaga contains various elements e.g. coumarins and furocoumarins, the most important of which are khellin and visnagin.[15] Xanthotoxin (methoxsalen) and ammidin (imperatorin), 2 furocoumarins from khella fruits, have been discovered.[16] Two furoquinoline alkaloids with varying cytotoxic activity have been isolated from A. majus.[17] Biosynthesis of khellin, visnagin, furocoumarin, and visnadin have been investigated.[18] Solubility and dissolution studies of khellin also have been described.[19] Numerous reports regarding khella constituents, their concentrations at various stages of maturity,[20,21] presence in certain plant parts,[22] and interactions with different plant extracts are available.[23] All of these reports illustrate the complexity of using the raw plant in treating kidney diseases without taking into account the various conditions which affect its active ingredients concentrations and potential cytotoxicities.

The usage of oral khella as a therapy is not as safe as it might sound and limited by its potential cytotoxicity.[24–28] In humans, two studies have been conducted; the first investigated the utilization of oral khellin to reduce blood lipids and the second studiedthe effects of khellin in vitiligo.[24,25] Researchers observed that gastro-intestinal side-effects were observed frequently (29% of patients in the vitiligo study) and, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also reported during therapy (7% to 14%).[24,25] One patient (4%) reported a serious complication in the form of temporary reduction in the visual acuity that resolved upon discontinuation of treatment.[24] Other potential adverse reactions have been reported including dizziness, constipation, headache, itching, insomnia, and lack of appetite.[29] Khella has been associated with the development of severe ophthalmologic changes, particularly pigmentary retinopathy.[30,31] Patients receiving khella or its extracts should be monitored for ophthalmologic changes.

The furocoumarins (psoralens) found in khella plant may cause photosensitization and dermatitis.[26] One study reported fourirritant active ingredients from khella seeds and investigatedthe mechanism of action of their potential contact dermatitis.[28] A case report described a case withallergic rhinitis and contact urticaria as a result of exposure to khella during cultivation in a florist shop. She had positive pinprick test as well as positive immunoglobulin E levels specific to khella. Once she stopped working as florist, the patient recovered and remainedasymptomatic.[27] In our case, the patient used to drink a big bottle of boiled khella seeds every day, hoping to improve his kidney function. In a study on rats, the investigators determined the lethal doses of khellin; the median lethal dose was 3.6 gm/kg-body weight for intraperitoneal administration and 10.1 gm/kg-body weight for oral administration.[32,33] In conclusion, we are reporting for the first time a case of acute kidney injury that might be of multifactorial etiology including pre-renal as a consequence of heavy diuresis and gastrointestinal upsets, after use of khella as well as direct renal toxicity as evident by eosinophilic interstitial nephritis seen on renal biopsy.

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Conflicts of interest

The author declares there is no conflict of interest.

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