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## **Unusual Cause of Rhabdomyolysis Causing Acute Renal Failure: *Achillea millefolium* and *Rheum palmatum* Plants**

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### **Authors' contributions**

This work was carried out in collaboration between all authors. Author TS wrote the draft of the manuscript. Authors TS and YK managed the literature searches. Author MS designed the figures, managed literature searches and contributed to the correction of the draft. Author TS provided the case, the figures and supervised the work. All authors read and approved the final manuscript.

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**Case Study**

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### **ABSTRACT**

**Introduction:** Rhabdomyolysis is a frequent disorder resulting from many different causes which may be apparent from the history, e.g. trauma, heavy exercise, intoxications. It contains both clinical and biochemical components. Acute kidney injury is probably the most significant and the most feared complication of rhabdomyolysis. Even though cases with rhabdomyolysis due to herbal medicine or extracts are reported; rhabdomyolysis because of consumption of plant itself is quite rare.

**Case Presentations:** Acute kidney injury in two otherwise healthy patients secondary to rhabdomyolysis is presented. Etiologic agents were determined as ingestion of plants named as

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“Yarrow” (*Achillea millefolium*) and “Turkish Rhubarb” (*Rheum palmatum*) growing especially in rural Southeastern Anatolia region of Turkey after all other possible causes of rhabdomyolysis was ruled out. Hemodialysis was performed to both patients temporarily. Kidney damage was recovered eventually.

**Conclusion:** Herbal medicine and/or plants usage should be addressed in patients with rhabdomyolysis and acute kidney injury after all known etiologic reasons are ruled out.

**Keywords:** Rhabdomyolysis; acute kidney injury; plants; herbal medicine.

## 1. INTRODUCTION

High concentrations of many medications or their metabolites take a long journey along the glomeruli and tubules since they metabolize, concentrate, and excrete them [1,2]. Therefore, as with prescribed medications, many dietary supplements have been associated with nephrotoxicity, either as a direct toxic effect, or secondary to liver dysfunction, rhabdomyolysis (RML), or nephrolithiasis.

Rhabdomyolysis is a syndrome in which muscle necrosis and release of intracellular muscle constituents into the circulation are seen. The most common symptom is muscle pain while elevated creatine kinase levels and myoglobinuria are main the laboratory abnormalities. Its clinical severity is so heterogeneous that asymptomatic elevations of creatine levels is at one end and severe life – threatening disease with acute kidney injury (AKI) is at the other end of the clinical spectrum [3,4].

There are multiple potential causes of RML such as traumatic (eg, crush syndrome), no traumatic exertional (eg, hyperthermia, or metabolic myopathies) and no traumatic nonexertional (eg, alcoholism, drugs or toxins, infections, or electrolyte disorders) muscle compression [5-8]. Although rare, there are also case reports of RML due to consuming certain herbal products, alone or in association with drugs [9-16].

A number of cases with RML due to herbal drugs and extracts have been published, whereas we herein, for the first time, report on two patients who developed RML and AKI owing to consumption of herbs that grow naturally in Southeast of Turkey.

## 2. CASE 1

Twenty-three years old woman living in Malatya (a city in Southeastern Anatolia) presented to our emergency service complaining of generalized edema, dyspnea and decrease in urine for

approximately one week. When asked for history, we have learned that she brew and drunk yarrow tea (*Achillea millefolium*, a naturally growing plant in Eastern Anatolia) with the hope of healing her ovarian cyst. The history was not significant for any suicidal attempt. Nausea, vomiting and flank pain developed 2 days after drinking yarrow tea, and the laboratory tests obtained from a local hospital in Malatya were as follows; serum blood urea nitrogen (BUN): 73 mg/dL, creatinine: 7 mg/dL, aspartate transaminase (AST): 1233 U/L, alanine transaminase (ALT): 593U/L, lactate dehydrogenase (LDH): 2622U/L, creatine kinase (CK) was higher measurement range. Intravenous isotonic saline and bicarbonate were started there, and periorbital and pretibial edema with dyspnea developed on the 3<sup>rd</sup> hospital day. The patient refused treatment at local hospital and admitted to our emergency service. She did not have a history of any disease and did not use any drugs. On admission to nephrology service; she appeared dyspneic with pretibial and periorbital edema. Systemic physical examination revealed that blood pressure was 150/95 mmHg, pulse rate at 90 bpm, diminished lung sounds at the bases of the lungs and crackles at both mid lung fields. Chest X ray examination was consistent with pleural effusions up to mid levels of the both lungs. Laboratory tests were serum urea: 181 mg/dL, creatinine: 12.4 mg/dL, AST: 1526 U/L, ALT: 644 U/L, LDH: 2402 U/L, CK: 15176 U/L, hematuria and pyuria in automated urine analyzer (Table 1). On urinary ultrasound, kidney sizes were normal but echogenicity of both of them were increased to grade 1-2. Daily urine output was 50 mL per day initially. RML complicated with oliguric AKI and hypervolemia was our diagnosis. Non-tunneled hemodialysis catheter was inserted into the right femoral vein. After having one session of hemodialysis, kidney biopsy was performed showing features of acute tubular necrosis. Until 6<sup>th</sup> day of hospital admission, 4 sessions of hemodialysis was performed and the daily urine output increased up to 500 mL gradually. A few days later, the catheter was removed and she

was discharged home with the laboratory values returned to normal.

**Table 1. Biochemical serum data of both cases of rhabdomyolysis at their admission to the hospital**

Parameters	Case 1	Case 2
Urea (mg/dL)	181	222
Creatinine (mg/dL)	12.4	18.7
Aspartate transaminase (U/L)	1526	215
Alanine transaminase (U/L)	644	56
Lactate dehydrogenase (U/L)	2402	2121
Creatine kinase (U/L)	15176	3587

### 3. CASE 2

Twenty years old shepherd living in Bitlis (a city in Southeastern Anatolia) admitted to our hospital complaining of widespread arthralgia, nausea and abdominal pain for 6 days. The patient's history was significant for ingestion of naturally growing raw Turkish Rhubarb (*Rheum palmatum*) 6 days ago while grazing the sheeps in the rangeland, and nausea abdominal pain just a few hours after the ingestion of them. He did not have history of any disease and drug usage, suspicion of suicidal attempt After admission on our service, at physical examination, blood pressures was 130/80 mmHg, pulse rate at 88 bpm, and the rest of the physical examination was normal. Laboratory tests were as follows; serum urea: 222 mg/dL, creatinine: 18.7 mg/dL, AST: 215 U/L, ALT: 56 U/L, creatine kinase: 3587 U/L, LDH: 2121 U/L, potassium: 4,8 mEq/L, hematuria, pyuria, proteinuria in automated urine analyzer (Table 1). Grade 1 to 2 increases in echogenicity of both kidneys was seen on urinary ultrasound scan. Our diagnosis was AKI because of RML. Intravenous saline and bicarbonate infusion was started immediately. Two sessions of hemodialysis were performed due to uremic symptoms. Urine output was increased in a few days with gradual decrease in serum creatinine levels concomitantly. Therefore, kidney biopsy was not performed and laboratory tests returned to normal ranges within 2 weeks after his presentation.

### 4. DISCUSSION

We presented otherwise previously healthy two patients with RML complicated with severe AKI. Both of them had history of ingestion of two naturally growing plants in the highlands of

Southeastern Anatolia. Evaluation of all other possible causes of RML resulted in nothing special. They did not have a suicidal attempt, signs of an infection, history of trauma, use any other medicine, or have heavy exercise. As a result, the only possible reason for this condition was thought as the natural plants' ingestion in both of them. One patient has kidney biopsy consistent with acute tubular necrosis while the other did not have it because of rapid recovery of kidney functions. Renal recovery was complete with creatinine levels returning to normal levels and urine examination showing no abnormality.

Yarrow (*Achillea millefolium*) is known as an antiseptic, contracting, blood purifier, diaphoretic, diuretic, and stimulant [15,17,18] plant. It contains isovaleric acid, salicylic acid, asparagin, sterols, flavonoids, bitters, tannins, and coumarins. Yarrow contracts skin and have anti-inflammatory properties not only to the skin but also to the stomach's and bowels' mucous membranes. It helps women in many ways including decrease in menstrual bleeding by increasing the tonicity of uterus and decrease in menstrual pains by its anti-inflammatory property. Yarrow contains high concentrations of tannins [15,19]. Sorokin et al. [9] reported an association between ingestion of pomegranate while taking rosuvastation and RML. Pomegranate juice contains high concentrations of antioxidants called polyphenols, anthocyanins and tannins. Grapefruit and pomegranate juice are known to inhibit intestinal cytochrome P450 3A4 and both of them contain plenty of tannins [9]. Although not proved, the cause of RML in our patient can also be the presence of high amounts of tannins in the Yarrow plant.

Rheum genus is from *Polygonaceae* family and contains approximately 60 perennial plants [20]. The genus includes the vegetable rhubarb (*Rheum rhabarbarum* or *Rheum x hybridum*). Rhizomes and roots of *Rheum officinale* or medicinal rhubarb are used to prepare drug rheum. This species is also native to Asia, as is the Turkish Rhubarb (*Rheum palmatum*).

In food preparation, leaf stems or petioles of plants are used. They produce some toxic substances. The first one is oxalic acid found in all parts of the plants but present in very low concentrations in leaf stems. The other ones are citric acid and anthraquinone glycosides those may be poisonous to human beings if leaf blades are ingested whether they are cooked or not and livestock if consumed in excessive amounts [21].

Turkish Rhubarb sprouts are found more abundantly in the highlands of Van and Hakkari (two cities in Eastern Anatolia). As a common habit, the roots of this plant are collected, peeled off and eaten in spring.

*Rumex crispus* (yellow dock) is taken as an antibiotic, laxative and anti-inflammatory aid, contains anthraquinone glycosides, tannins, and oxalates [22]. On autopsy of an adult male ingesting 500 grams of yellow dock, hepatocellular necrosis, swelling and retraction of the glomeruli, and calcium oxalate crystal deposition in the renal cortex are seen [23]. Vanderperren B et al. [24] also published a female patient ingesting senna anthraquinone glycosides chronically who had acute liver and kidney failures requiring admission to intensive care unit. There are no available human data about relationship between sennosides and nephrotoxicity. However, experimental models suggest that kidneys may show anthraquinone derivatives' deposits [24]. Oxalic acid, citric acid and especially anthraquinone glycosides, which are the constituents of Turkish Rhubarb, may be responsible from RML and the resultant AKI that occurred in our patient.

RML would require hospitalization when the possible complications like electrolyte imbalance, cardiac arrest, AKI are regarded. Treatment options are urinary alkalinization, maintenance of oral fluid intake, careful intravenous hydration, mannitol, diuretics if needed. In severe cases, hemodialysis may be required [25]. In these two cases, medical treatment was also given initially; however, hypervolemia and uremic symptoms urged hemodialysis in each patient.

We suspected that oxalic acid, citric acid and especially anthraquinone glycosides present in the Yarrow plant and in Turkish Rhubarb as cause of RML in the two patients. It will be interesting to verify our suspicions.

## 5. CONCLUSION

In cases where the causes of RML and AKI are not apparent, we suggest that questioning for ingestion of herbal medicine and/or raw plants may point to the culprit.

## CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

## ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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