



Acute Interstitial Nephritis in a Patient Using Herbal Product

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Authors' contributions

This work was carried out in collaboration between all authors. Author EPG managed literature searches, wrote the first and final draft of the manuscript. Author FGS contributed to the writing and helped in making of the final draft. Authors EUCA, RMQ and HLG helped in manuscript corrections and literature researches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Acute interstitial nephritis is one of the most common causes of acute kidney injury. Many herbal products have been associated with kidney damage but the Melaleuca product has never been reported in medical literature.

Presentation of Case: A 59-year-old woman arrives to the emergency department with nausea and generalized discomfort. Relevant medical history of hypertension with captopril and a non-specified anxiety disorder with paroxetine and clonazepam. Patient mentioned Melaleuca's Recover AI® consumption and ciprofloxacin suspended 10 days before arriving to the emergency department. The rapid deterioration of renal function in the context of a previously healthy patient made it necessary to take a biopsy to establish a diagnosis and start treatment with

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immunosuppressant's, obtaining a good response with a favorable clinical evolution.

Discussion: The use of herbal products is increasing in many countries and patients do not consider these as potentially harmful. These products have been associated with liver damage and in rare cases, such as ours, to kidney damage.

Conclusion: Physicians are obligated to interrogate intentionally about the consumption of herbal products and always consider them as a possible etiology of acute kidney injury secondary to acute interstitial nephritis.

Keywords: Acute interstitial nephritis; renal biopsy; herbology product; acute kidney injury acute interstitial nephritis; renal biopsy; herbology product; acute kidney injury.

ABBREVIATIONS

AIN : Acute interstitial nephritis

AKI : acute kidney injury

1. INTRODUCTION

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury (AKI), particularly in hospitalized patients. It has been implicated in 5-15% of the hospitalized patients admitted for AKI [1]. The classical triad of: fever, rash and eosinophilia are not always present therefore AIN should be considered in patients with a unexplained progressive rise in serum creatinine [2]. The following is a case report of herbal induced acute interstitial nephritis secondary to Recover AI ® consumption.

2. CASE REPORT

A 59-year-old woman comes to the emergency room because of nausea and generalized discomfort. Referred arterial hypertension diagnosed 8 years ago in control with captopril 25 mg tid, which is in control, and a non-specified anxiety disorder treated with paroxetine and clonazepam. With intentional interrogation patient alluded Melaleuca's Recover AI ® consumption 1 tablet daily, mentioning taking it for approximately a month. As relevant recent events she mentioned semiliquid evacuations 15 days ago, which was treated with ciprofloxacin that resolved by the fourth day and treatment was suspended about 10 days before arriving to the emergency department. Because of this condition, a blood count and biochemical profile were performed, where a creatinine of 1.8 mg/dL was reported in an external laboratory.

The vital signs and neurological, cardiac, pulmonary and abdominal examination were reported as normal upon admission. No lymphadenopathy or visceromegaly were found. The following laboratories were requested:

hemoglobin 12.4 g/dL, leucocytes 6.900/mm³ with a normal differential and platelets 298,000/mm³, venous gasometry with pH 7.30, pCO₂ 36 mmHg, HCO₃ 17.6 mmol/L, lactate 9 mg/dL (metabolic acidosis with a high anion gap), sedimentation rate 51 mm/hr, sodium 138 mmol/L, potassium 4.19 mmol/L, chlorine 94.5 mmol/L, uric acid 14.5 mg/dL, calcium 9.1 mg/dL, phosphorus 9 mg/dL, magnesium 2.7 mg/dL, urine test reported cloudy urine with hemoglobin positive, abundant sediment, erythrocytes 1-3/field, leukocytes 5-8/field. It was also requested quantification of antistreptolysin O, C reactive protein, immunoglobulin IgE, C₃, C₄ were reported within normal range. Antinuclear antibodies, anti-cyclic citrullinated peptide IgG, rheumatoid factor, p-ANCA and c-ANCA were negative. Serum protein electrophoresis was reported as normal. Since all the results were negative and the creatinine increased to 9.6 mg/dL on the next day and a cause for the AKI was still not determined, the patient was submitted to an ultrasound-guided needle biopsy which was performed without complications. The patient initiated treatment with methylprednisolone because of a probable diagnosis of rapidly progressive glomerulonephritis.

Biopsy findings reported light microscopy of mild chronic interstitial inflammation with dispersed eosinophils suggestive of acute interstitial nephritis and atherosclerosis. Immunofluorescence and electron microscopy were reported as normal. The findings of the renal biopsy can be observed in Figs. 1-3. The patient was diagnosed with interstitial nephritis and started treatment with methylprednisolone 500 mg IV every 24 hours for 3 doses, amlodipine 5 mg PO every 12 hours, allopurinol 100 mg PO every 24 hours and cyclophosphamide 1.2 gr IV as a single dose. Patient showed a favorable response with decrease of the creatinine and was discharged with losartan 50 mg PO every 24 hours and prednisone (Fig. 4).

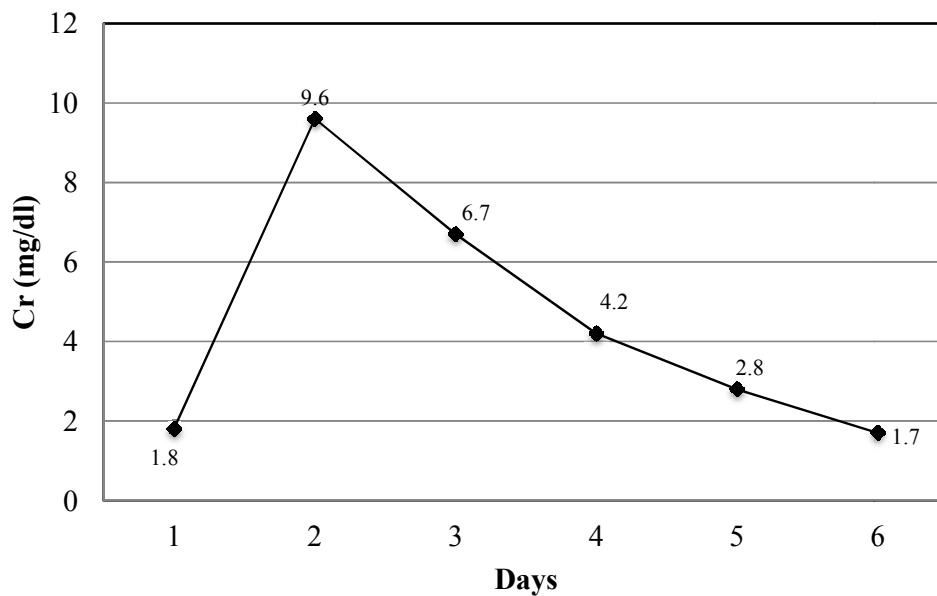


Fig. 1. Creatinine levels

Evolution of creatinine levels before and after initiation of immunosuppressive therapy on day 2

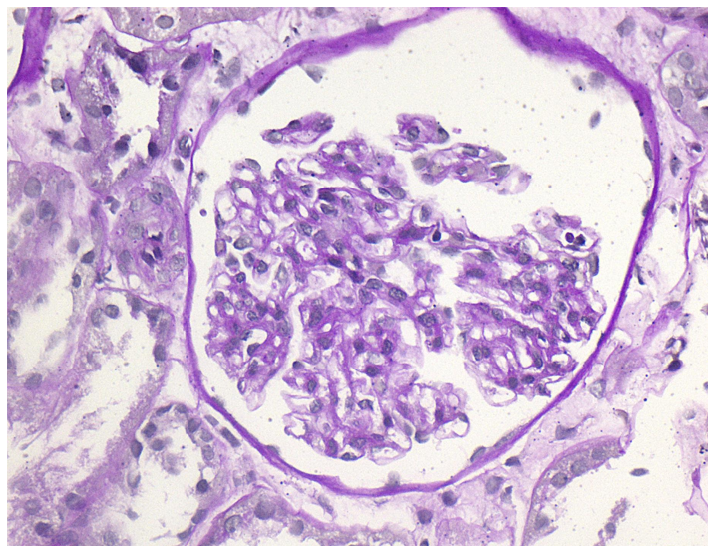


Fig. 2. Normal glomerulus

Histological section stained with Schiff periodic Acid seen at 40x showing a normal glomerulus.

3. DISCUSSION

Several herbal medications have been reported to cause renal damage [3]. Traditional remedies are of common use worldwide being about 80% in some populations [3]. It has been noted that socioeconomic, cultural and local health practices influence greatly in the consumption of

herbal products. In recent years the consumption of these compounds has increased, regardless of the socioeconomic status of the population [3]. All herbal medications are considered by consumers as “natural alternative remedies” which are safe and usually do not report their use to doctors [4]. Therefore the importance of including herbal medications as part of the

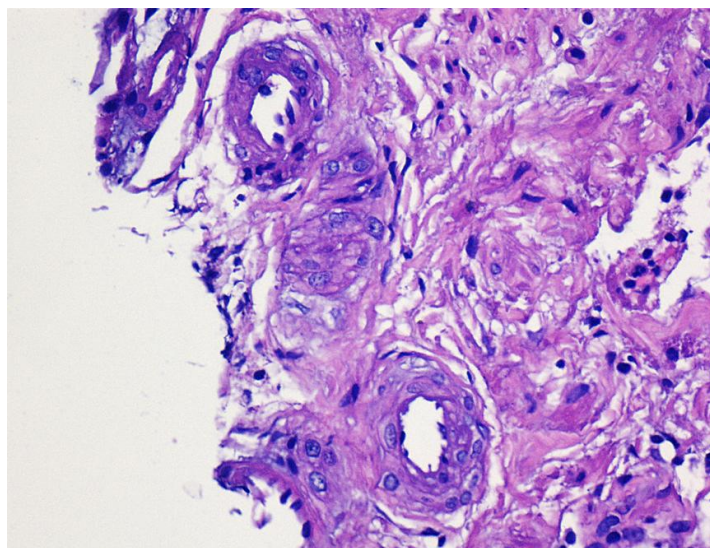


Fig. 3. Arteriosclerosis

Histological section stained with Schiff Periodic Acid seen at 40x shows blood vessels with hyperplasia and fibrosis of the intima (arteriosclerosis).

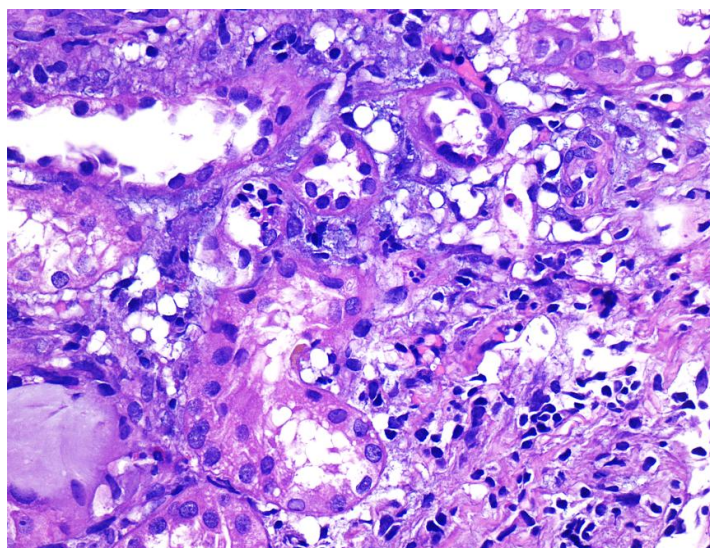


Fig. 4. Interstitial nephritis

Schiff Periodic Acid stain seen at 40x shows Interstitial infiltrates formed by eosinophils and lymphocytes.

medications a patient might take and intentionally ask about them [5]. The renal involvement with the use of herbal medicine is: AKI, defects in tubular function, electrolytic alterations, systemic hypertension, chronic renal disease, renal papillary necrosis, urolithiasis and urothelial malignancy [3].

AIN is a very common cause of AKI, with a prevalence being found in 15-27% of patients in whom kidney biopsy was performed for AKI [6].

Clinically AIN can be nonspecific presenting with nausea, vomiting, malaise and fever while laboratory wise it's of rapid onset with elevated blood urea nitrogen and creatinine with proteinuria, sterile pyuria, hematuria and sometimes eosinophilia. The classical triad of rash, fever and eosinophilia is only reported in 10% of the patients [1]. Retrospective series of 128 patients reported 70% of the AIN being drug induced, 15% of these had rash, 27% fever and 23% eosinophilia [1]. Our patient only referred

generalized discomfort and nausea with pyuria, hematuria and elevated serum creatinine without eosinophilia in initial laboratory studies. After various causes of our patient's AKI were investigated and excluded, a drug-induced AIN was considered.

The causes of AIN throughout the years have changed. Initially infections were the most common causes but nowadays drugs are responsible for most cases. The increase in the prevalence of drug induced AIN can be due to the widespread use of antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and other medications [6]. A study made by Muriithi et al. which included 133 patients (45 being > 65 years and 88 between 18 and 65 years) concluded that the most common cause of AIN regardless of age is drug-induced with 39 (87%) and 56 (64%) cases in each group. In the patients greater than 65 years, antibiotics and proton pump inhibitors were the most frequently involved drugs with 54% (n=21) and 20.5% (n=8) cases whereas in patients under 65 antibiotics and NSAIDs were the most common causal agent with 47% (n=26) and 16% (n=9) cases, respectively [6]. Most herbal mechanisms of renal damage are unknown but perhaps the best-elucidated mechanism of nephrotoxicity secondary to the use of unadulterated herbal remedies is aristolochic acid [6].

However, other mechanisms include interactions of herbs and drugs and the contamination of herbal products with heavy metals or adulterants [6]. Recover AI ® is a herbal medication said to promote healthy inflammatory response that contains devil's claw extract (*Harpagophytum procumbens*), ginger root extract (*Zingiber officinale*), chokeberry fruit extract (*Aronia melanocarpa*), angelica gigas (*Dang Gui*), turmeric (*Curcuma longa*) and green tea leaf extract (*Camellia sinensis*). Any of these components could be the cause of the AKI. To our knowledge there are no reported cases of nephrotoxicity due to Recover AI ® or any of its components.

Another thing to consider is that our patient consumed ciprofloxacin, which have also been reported to be nephrotoxic [7,8]. A case-control study approved by the University of Florida's Institutional Review Board studied the risk of AKI associated with the use of fluoroquinolones focusing on outpatient management with these drugs. The discontinuation of ciprofloxacin in our patient 10 days prior admission, according to the

study, includes her in the "recent user" category (last use of quinolones 8-60 days before hospitalization). The study concluded that current use of fluoroquinolones increased the risk of AKI (RR 2.18, 95% CI 1.74-2.73) but recent use had no significant association (RR 0.87, 95% CI 0.66-1.16) [8]. In our patient, the suspension of ciprofloxacin 10 days before arriving to the emergency department excludes this possibility.

Interstitial nephritis is one of the common histopathologic findings that result from direct toxicity of the remedy, which induces inflammation, idiosyncratic or allergic reaction [3]. As mentioned previously the renal biopsy is required to establish a definitive diagnosis of acute interstitial nephritis and even more drug induced [2]. The main pathological findings are interstitial infiltrates with a predominance of lymphocytes and monocytes and a smaller number of eosinophils. The presence of a considerable amount of eosinophils favors a diagnosis of drug-induced AIN [2]. The immunofluorescence and electron microscopy must be reported as negative for immune complexes. These results are compatible with drug-induced AIN and all were reported in our patient [2].

The most important aspect of AIN includes the discontinuation of the causative agent. Also, the probability of recovery depends on the duration of the kidney injury prior to diagnosis and initiation of treatment. Some authors recommend the use of steroids and other immunosuppressive drugs based on the hypothesis that renal inflammation is caused by an allergic process but some contradictory evidence exists questioning these medications [2,6]. Other immunosuppressive drugs have also been utilized such as mycophenolate mofetil [5]. Little evidence has been reported with the use of cyclophosphamide but its utility in lupus nephritis supports its use. Our patient responded favorably with the discontinuation of the herbal medication, steroids and cyclophosphamide.

4. CONCLUSION

All herbal medications are a potential cause of AIN therefore a high index of suspicion should be taken in account. The most important actions to prevent AIN by herbal medications are: a better communication between patients and doctors about the use of herbal medicine, health care

professionals should be informed of herb-drug interactions and invite their patients to discuss herb medicine use and most importantly doctors should question their patient about the use of herbal medicines.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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