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Tubular Interstitial Nephritis Secondary to Herbal Consumption: Case Report and Literature Review

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ABSTRACT

Acute tubular interstitial nephritis is a form of immune-mediated renal injury characterized by infiltration of immune cells in the renal tubulointerstitium, leading to oliguric or non-oliguric acute kidney injury. It manifests with systemic arterial hypertension, foamy urine, and sometimes with secondary anemia if there is progression to chronic renal disease. The diagnosis of certainty is made by biopsy, the initial treatment consists of identifying and removing the triggering agent to avoid further exposure to toxins, management of the acute renal lesion and in some cases, it may be decided to start corticosteroids to avoid progression to end-stage chronic kidney disease. We present the case of a 24-year-old female patient with a history of consumption of unspecified herbal medicine for aesthetic purposes 3 years prior to our evaluation, who debuted with hypertensive emergency manifested by hypertensive retinopathy, hypertensive renal vasculopathy and tubulointerstitial nephritis, successfully treated with the withdrawal of the aggressor agent, angiotensin converting enzyme inhibitors, nitrates and corticosteroids. After 6 months of follow-up, the patient is asymptomatic and with total recovery of the renal disease documented by normal creatinine in laboratory tests.

KEYWORDS: Tubulointerstitial nephritis, Acute kidney injury, Chronic kidney disease, Renal tubulointerstisium, Corticosteroids.

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INTRODUCTION

Acute tubulointerstitial nephritis (ATIN) is defined as an acute renal lesion characterized by lymphocytic infiltration at tubulointerstitial level, generally secondary to drugs, toxins, infections, autoimmune diseases, and when no apparent origin is found, it is called idiopathic[1,2]. The most frequent etiology is secondary to drugs, which is the cause of approximately 60-70% of cases [3].

We believed that drugs are the most common etiology due to the easy access to both allopathic and homeopathic medications, whether purchased under health prescriptions or autonomously by the patients. The kidney is the site of excretion metabolism in most drugs, so the kidney is the site of affection par excellence, leading to multiple harmful mechanisms that cause: Acute tubular lesion, nephrolithiasis, rhabdomyolysis and even with concomitant liver involvement if hepatorenal syndrome develops[4,5].

In the early 1990s, nine cases of rapidly progressive fibrosing interstitial nephritis were described in Belgium in young women who were apparently treated with the plants Stephania tetrandra and Magnolia officinalis at a weight loss clinic in Brussels, Belgium [6]. Later was discovered that S. tetrandra had been inadvertently replaced by another plant "Aristolochia fangchi", that contains aristolochic acid, which is a nephrotoxic and carcinogenic alkaloid plant in humans and animals [3,6]

Likewise, some roots, stems or dried leaves have been proposed as nephrotoxic agents, alone or as part of complex recipes as home remedies for asthma, coughs, hemorrhoids, arthralgias, edema, headache, abdominal pain, ulcers, urinary tract infections and for snakes or insect bites[5].

The main antecedent for the suspicion diagnostic in this type of patients that presents acute tubulointerstitial nephritis is the history of consumed any of the previously mentioned products. However, there are cases in which the patient does not remember or not mention the ingestion of the toxic substance, debuting with arterial hypertension, anemia, low-grade proteinuria, glycosuria, and insignificant urinary sediment, with posterior progression to rapid deterioration of renal function [7], which makes it difficult to reach the diagnosis and therefore this entity is underdiagnosed.

The long-term prognosis is generally favorable with a complete renal recovery if the offending agent is identified early, but some patients may culminate in the development of chronic kidney disease (CKD) [3].

CASE REPORT

We present a case of a 24 year old female patient, with no family history or chronic degenerative diseases of importance for current condition, she only refers to being a social drinker and smoker, and with the aim of reducing weight for aesthetic purposes in the 3 years before our assessment she began to consume herbal capsules that had the Aristolochia plant as the principal component, also knowns as Cocolmeca plant in Mexico, in addition to another medications like L-carnitine, antioxidants, and even metformin and liraglutide.

She began her current condition with the presence of hematomas that appeared after she received a minor accidental trauma, moderate intermittent oppressive, bitemporal and retroorbital headache with an 4/10 intensity lasting 1 to 2 hours, without nausea or vomiting, which lightly improved with analgesics, with posterior apparition of blurred vision, so she decided to go for a check-up at our center, deciding to hospitalize her because an elevated blood pressure of 260/100mmHg, the initial laboratory tests reported: Leukocytes 9. 2 K/ul, hemoglobin 10.6 gr/dl, hematocrit 32%, platelets 83 K/ul, ALT 10.1 U/L, AST 29.3 U/L, BD 0.24 mg/dl, BI 0.39 mg/dl, BT 0.63 mg/dl, CPKT 66 U/L, CPkMb 21 U/L DHL 1046 UI, urea 79 mg/dl, bun 37 mg/dl, creatinine 2.47 mg/dl. Because the presence of renal injury, the initial suspicion diagnosis at the first instance is that damage was secondary to the hypertensive emergency; as an initial therapeutic approach, antihypertensive treatment was decided (angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, potassium sparing and alpha adrenergic blockers) and apparent control was achieved after 7 days of pharmacological adjustments. However, despite the antihypertensive control obtained, our patient continued presenting clinical data suggestive of hypertensive retinopathy and hypertensive nephropathy, so she was evaluated by the ophthalmology service who confirmed structural changes secondary to hypertensive retinopathy, as well as after new control of serum creatinine with no resolution of the renal injury, so we initiated the diagnostic approach of the renal injury. Multiple studies were performed, including 24-hour urine protein with non-nephrotic proteinuria range (187mg/dl in 24 hours), 24-hour urine creatinine clearance (51.79ml/min), without presenting dysmorphic erythrocytes in urinary sediment, so it was decided to perform renal doppler ultrasound and abdominal computed tomography with the aim of demonstrates a structural cause of the renal lesion or renal changes suggestive of chronic disease, however, given normality in both studies, these two possibilities were ruled out (Figs. 1,2).

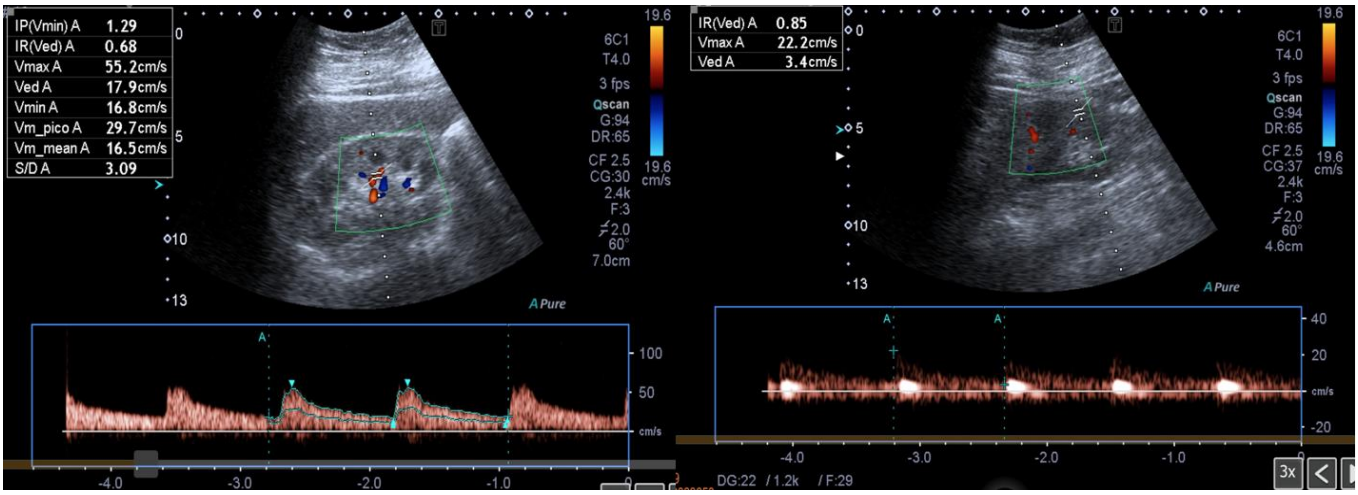

Figure 1. Renal Doppler ultrasonography, both kidneys are observed with preserved morphology and echogenicity, without evidence of lesions. On color Doppler test, no evidence of alterations in both renal arteries and veins, of adequate caliber. Doppler study with preserved flow morphology, color flow and normal spectra.

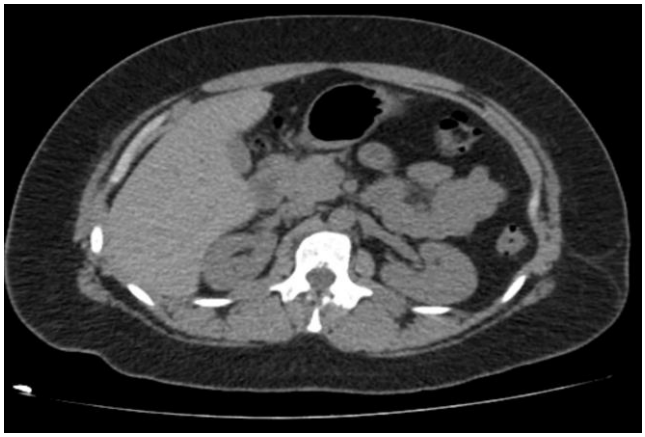

Figure 2. Abdominal computed tomography in axial section. Both kidneys shows normal morphological characteristics, there are no evidence of chronic renal disease.

Therefore, the diagnostic suspicion was oriented towards an autoimmune condition given the characteristics of the patient, so immunological markers were requested, only antinuclear antibodies were positive with a result 1:160, management were initiated with methylprednisolone boluses of 1 gram every 24 hours for 3 days presenting partial response, which led to protocolize our patient with a renal biopsy.

The biopsy reported tubules with sphacelate epithelium and mild tubulitis, an interstitium with an extensive chronic inflammatory exudate, blood vessels with middle layer fibrosis and decreased lumen caliber, being confirmed a diagnosis of tubulointerstitial nephritis and hypertensive vasculopathy (Fig. 3 y Fig. 4).

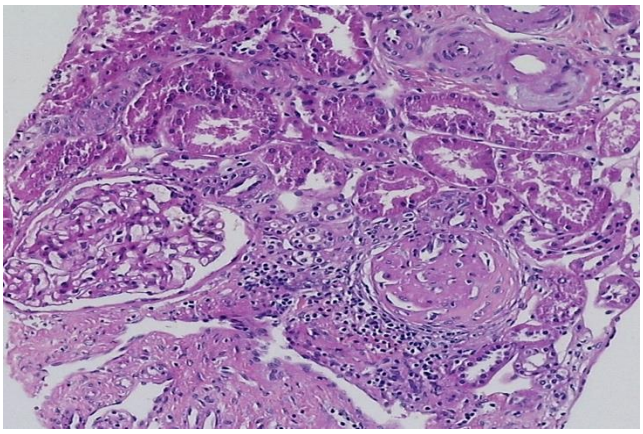

Figure 3. Histopathological staining with H&E 100x. At the left we can see a normal glomerulus, at the right a sclerosed one, in the lower part a chronic inflammatory infiltrate, and in the upper part capillary blood vessels with fibrosis are observed.

So due to the history of the consumption of medicinal herbs for aesthetic purposes, so due to the components of the Aristolochia plant, and the documented evidence of its association with the development of tubulointerstitial nephritis, we suspected that this was the cause of the deterioration of kidney function, so we decided to suspend the offending agent.

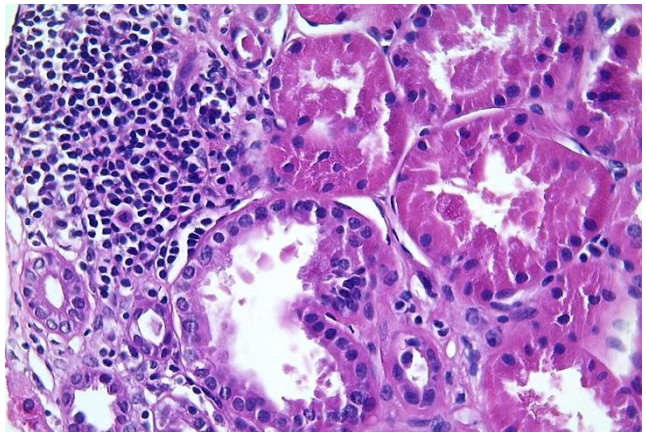

Figure 4. Histopathological staining with H&E 400x. At the right a tubular epithelium with sphacelating, at the left mild tubulitis and intersticium with chronic inflammatory exudate and inflammatory cells are seen.

After 6 months follow-up, a significant improve can be seen in our patient, without the presence of the previous kidney damage, returning to her basal renal function at the creatinine levels presented to date 1.1mg/dl, fully evidencing that such renal damage was secondary to the consumption of the Aristolochia plant.

DISCUSSION

ATIN, as previously mentioned, is a form of immune-mediated renal injury that in most cases manifests as an acute kidney injury and can even presents with non-impaired uresis [1,2] Among its multiple etiologies, the main one is secondary to drugs, especially non-steroidal anti-inflammatory drugs, antibiotics, diuretics, and chemotherapeutic. If they are not identified and withdrawal, they continue provocating the characteristic interstitial inflammation, allowing it to generate the chronic interstitial changes and sometimes the subsequent development of CKD [2].

Drugs represent approximately 70% (perhaps as much as 90%) of the related causes, followed by infections (16%), tubulointerstitial nephritis with uveitis (5%) and sarcoidosis (1%), while 8% are idiopathic or related with less common etiologies like the herbal consumption [1,8]

According to data from the World Health Organization (WHO), 80% of the world's population chooses traditional medicines or even curative plants over the medicines that are produced in a pharmacy and one of the reasons for this widespread use is the assumption that they are natural products and therefore, "secure". But traditional plants or medicines contain pharmacologically active ingredients, some of which have been associated with adverse effects [6]

Drug-induced ATIN usually begins 7 to 10 days after drug exposure, the risk is not dose-related and is compatible with an underlying immunologic mechanism [9]. However, in

cases related to herbal medicine, the time of presentation of ATIN after the onset of consumption is not well determined since these are consumed in non-homogeneous amounts in each intake, in addition to the fact that each specimen has a different amount of the toxicant. This contrast can be seen in the previously mentioned case in which the toxicity of the herb was not seen until 3 years after the onset of its consumption.

Among the plants that can cause nephrotoxicity, the most important are digitalis *(Digitalis purpurea)*, quinine *(Cinchona ledgeriana)*, salicylate *(Salix alba)*, taxol *(Taxus brevifolia)* and artemisinin *(Artemisia annua)* [H]; however, recently special attention has been paid to Chinese herbs since they generate aristolochic acid (AA) nephropathy, as in our case.

In Mexico, several medicinal plant species belonging to various genera, such as Aristolochia, Dioscorea and Milleria, are also known by the common name of "Cocolmeca" [10].

AA is a generic term describing a structurally related compounds that are found in the plant family *Aristolochiaceae* which can induce oxidative stress by interacting with antioxidant enzymes causing its defective activation, mitochondrial damage, progressive tubular toxicity and induction of apoptosis in renal tubular cells [6]

Among the main predisposing factors to toxin exposure and risk of renal injury are a high proportion of blood flow through the kidneys, their high metabolic activity, and reabsorption of glomerular filtrate by the renal tubules, which can result in a high concentration of the toxic agent at intracellular level [6]

Once inside the kidney, acute interstitial inflammatory reactions are associated with damage to the tubular interstitium caused by interstitial edema with infiltration of lymphocytes and plasma cells that compromise renal blood flow causing a decrease in the glomerular filtration rate and in some situations, interstitial fibrosis and tubular atrophy [2,8]

Initially, Aristolochia activates macrophages, contributing to inflammation by production of tumor necrosis factor (TNF) and transforming growth factor-beta (TGF-beta), which trigger a cascade of reactions that leads an activation of proinflammatory and profibrotic genes which then cause inflammation and secondary fibrosis [8].

Nephrotoxicity can manifest as acute kidney injury, proximal tubular dysfunction (glycosuria and increased excretion of low molecular weight proteins), hypertension, severe anemia, metabolic acidosis, small kidneys on renal ultrasound, and a high risk of urothelial malignancies, with estimated risk rates of 40% to 46% [7,11].

In the case of patients with pre-existing CKD, they may develop complications due to the use of herbal medicines; some examples are hemorrhagic complications induced by Ginkgo biloba, hypertension and hypokalemia induced by glycyrrhizinic acid, hyperkalemia induced by alfalfa or noni juice (*Morinda citrifolia*), among others [8].

Among the biochemical conditions, those found in the general urine examination stand out, which are pyuria, microscopic hematuria, glycosuria, low-grade proteinuria, elevated ESR and anemia [12,13]

Regardless of the underlying etiology, a kidney biopsy can confirm the diagnosis because the gold standard diagnosis is histopathological, in which it´s observed a characteristic inflammation, interstitial edema, tubulitis with presence of interstitial granulomas and tubulointerstitial inflammatory cell infiltrate (mainly lymphocytic and eosinophilic) that are more prominent at the corticomedullary junction [1,2], however a dominant eosinophil infiltrate is more suggestive of drug-induced kidney injury [13]

The first principle of effective therapy is the toxicity prevention, avoiding further exposure to nephrotoxin, and paying attention to fluid and electrolyte balance. Given the risks of CKD in these patients, longitudinal follow-up is necessary to monitor renal function [12]. When the time of drug exposure is prolonged, irreversible renal damage (interstitial fibrosis and tubular atrophy) may be present [14].

Given the immune-mediated nature of renal damage, corticosteroids are often indicated as early treatment was associated with benefit [1], therefore steroids should be initiated immediately after the diagnosis of ATIN to avoid subsequent interstitial fibrosis and incomplete renal function recovery [15].

There are no differences in renal function outcomes between high-dose intravenous corticosteroids versus 1 mg/kg/day oral prednisone for 2 to 3 weeks, followed by gradual tapering over 1 to 3 months [16].

Prognosis depends primarily on the cause of ATIN, in combination with treatment for systemic disease, timing of treatment, previous renal function, and clearance of any known offending agents.

CONCLUSION

Herbal medicines have had and continue has an important role throughout the world. A common belief is that most of people who use these medicines consider them to be natural and inexpensive as environmentally friendly and therefore non-toxic and non-aggressive to their health. However, at today there are multiple reports of toxicity secondary to natural products manifested differently depending on the affected organ being the severe renal affection as one of the most documented lesions, it should be warned that these compounds can cause serious adverse effects that can even threaten the life of the involved.

Systematic toxicological studies on herbal medicines, professional monitoring and strict quality control standards that are regularly used for conventional medicines are essential to reduce this toxicity damage.

In summary, herbal medicine consumption is an underrecognized and underreported cause of nephrotoxicity that should always be considered in the absence of a suggestive etiology of kidney injury even though ingestion of traditional medicine has not been documented. Nephrologists should always be encouraged to obtain a detailed history of supplements, the prescription drugs and herbal medicine, regardless of the ethnicity of the patients. Greater global awareness is important, because recognizing and managing this entity will help to build the evidence to develop more effective therapies and to inform to the general population of the latent injury that can exists if they consume these types of products and that being "natural" does not necessarily mean that they have no adverse effects.

CONFLICT OF INTERESTS

The authors have declared no conflicts of interest.

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