Liver injury induced by *Phyllanthus niruri* (chancapiedra), a natural remedy for urolithiasis

Lesión hepática inducida por *Phyllanthus niruri* (chancapiedra), un remedio natural para urolitiasis

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Abstract

Both drug-induced liver injury (DILI) and herb-induced liver injury (HILI) are a growing concern in contemporary healthcare that poses significant clinical challenges due to their varied etiology, clinical presentations, and potential life-threatening outcomes. We present the case of a 38-year-old male patient with a history of kidney stones who consulted for low back pain and hematuria. On admission he presented with jaundice, hepatomegaly, pain on palpation in the right iliac fossa and no signs of chronic liver disease, with abnormal liver function tests, which showed a hepatocellular pattern associated with hyperbilirubinemia. Biliary obstruction, portal thrombosis, autoimmune and viral hepatitis were ruled out, with negative autoimmune panel. The patient reported consuming an herbal remedy for kidney stones called "stone-breaking wine (chancapiedra)’, presumed to contain *Phyllanthus niruri*, five days before the onset of symptoms. A liver biopsy revealed acute hepatitis with mixed inflammatory infiltrate. Due to worsening of liver function tests and suspicion of idiosyncratic DILI, a therapeutic trial with corticosteroids was initiated, which resulted in clinical and liver profile improvement. The severity of this case reminds us of the need to increase follow-up by drug regulatory authorities, implement educational campaigns for patients, and inform the community about products with active alerts.

Keywords: drug induced liver injury, herbal medicine, *Phyllanthus*, hepatitis.

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Resumen
Tanto la lesión hepática inducida por drogas (DILI), así como la lesión hepática inducida por hierbas (HILI), son una preocupación creciente en la atención sanitaria contemporánea que plantea importantes desafíos clínicos debido a sus variadas etiologías, presentaciones clínicas y posibles resultados potencialmente mortales. Presentamos el caso de un paciente masculino de 38 años con antecedentes de cálculos renales que consultó por dolor lumbar y hematuria. Al ingreso presentó ictericia, hepatomegalia, dolor a la palpación en fossa iliaca derecha y no tenía signos de hepatopatía crónica, con pruebas de función hepática anormales, que mostraron un patrón hepatocelular asociado con hiperbilirrubinemia. Se descartó obstrucción biliar, trombosis portal, hepatitis autoinmune y viral, con panel autoinmune negativo. El paciente refirió haber consumido un remedio herbario para los cálculos renales llamado “vino rompe cálculos (chancapiedra)”, que se supone contiene Phyllanthus niruri, cinco días antes del inicio de los síntomas. Una biopsia hepática reveló hepatitis aguda con infiltrado inflamatorio mixto. Debido al empeoramiento de las pruebas de función hepática y la sospecha de DILI idiosincrásico, se inició un ensayo terapéutico con corticosteroides, que resultó en una mejoría clínica y del perfil hepático. La gravedad de este caso nos recuerda la necesidad de incrementar el seguimiento por parte de las autoridades reguladoras de medicamentos, implementar campañas educativas para los pacientes e informar a la comunidad sobre productos con alertas activas.

Palabras clave: enfermedad hepática inducida por sustancias y drogas, medicina de hierbas, Phyllanthus, hepatitis.

Introduction
Drug-induced liver injury (DILI) and herbal-induced liver injury (HILI) represent a growing concern in contemporary healthcare. DILI is characterized by liver damage resulting from drug abuse, a condition that poses significant clinical challenges due to its varied etiology, clinical presentation, and potentially life-threatening outcomes [1]. In contrast, HILI encompasses a variety of liver disorders associated with the use of herbal products and dietary supplements, which present a unique diagnostic and treatment complexities [2].

Despite advances in the understanding of these entities, they remain formidable problems in clinical practice. Both DILI and HILI can lead to severe liver failure, requiring prompt recognition and intervention. However, their diverse clinical manifestations often mimic other liver diseases, making early and accurate diagnosis a difficult task. In addition, the absence of specific biomarkers complicates their identification, further emphasizing the need for comprehensive surveillance and evaluation in clinical settings.

In Colombia, the epidemiology of DILI has been investigated in a prospective study conducted in a university hospital in Medellín, revealing an incidence rate of 6% [3]. However, DILI remains underdiagnosed and underreported, leading to uncertainty about its true prevalence. To address this problem, initiatives such as the Latin American DILI registry (LATINDILI) have been established to better estimate the frequency of DILI in our region [4].

This case report provides a comprehensive overview of DILI and HILI, covering aspects such as epidemiology, severity assessment, diagnostic approaches, and potential registries such as LATINDILI. Our goal is to improve the understanding and
treatment of these complex conditions, while emphasizing the importance of considering alternative remedies as potential hepatotoxic agents. Increased awareness and rigorous evaluation of herbal products and drugs are crucial steps in safeguarding patient welfare.

Case report

A 38-year-old Caucasian male patient from Soledad, Atlántico, came to the emergency department with a 5-day history of colicky right lumbar pain, with an intensity of 8/10, radiating to the ipsilateral flank and associated with macroscopic hematuria. His personal history included multiple episodes of renal lithiasis in the last 20 years. In addition, the patient reported jaundice of mucous membranes, palms, sclerae and skin of two days of evolution. Physical examination showed generalized jaundice, hepatomegaly and pain on palpation in the right iliac fossa without signs of chronic liver disease.

Laboratory tests showed predominant direct hyperbilirubinemia (total bilirubin: 16.19 mg/dL, direct bilirubin: 12.23 mg/dL), with elevated transaminases (aspartate aminotransferase (AST): 1,590.6 U/L and alanine aminotransferase (ALT): 614.3 U/L), and normal alkaline phosphatase (206.7 U/L), with an R factor of 8.9 consistent with a hepatocellular pattern. Coagulation times were within the normal range (prothrombin time (PT): 13.2 seconds, international normalized ratio (INR): 1.24, partial thromboplastin time (PTT): 28.3 seconds). Urinalysis revealed 3+ blood, 6 mg/dL urobilinogen, 4 mg/dL bilirubin and numerous red blood cells. Abdominal ultrasound showed hepatomegaly, pyelocaliceal ectasia and right nephrolithiasis, which was confirmed by urinary tract computed tomography as right distal ureterolithiasis with ipsilateral urinary tract dilatation.

During hospitalization the patient showed no signs of encephalopathy or INR greater than 1.5; however, during the following days bilirubin and transaminase levels progressively increased to a maximum of 22.25 mg/dL and 1,900 U/L, respectively (figures 1 and 2).

In the search for etiology, acute infection by hepatitis A, B, and C viruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus were ruled out. Similarly, autoimmune studies, including antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA), yielded nonreactive results. Doppler ultrasound of the portal vein revealed no signs of portal hypertension, effectively ruling out the possibility of portal thrombosis. Additionally, cholangioresonance imaging confirmed the absence of any biliary obstruction, indicating solely hepatomegaly.

Upon investigation, the patient revealed having ingested 5 days before his consultation two (approximately 720 mL) of a substance labeled “vino rompe cálcu- los (chancapiedra),” an indigenous product (figure 3), that is supposed to contain Phyllanthus niruri, to relieve pain due to recurrent nephrolithiasis; however, he had since stopped using it. In addition, the Colombian health regulatory agency INVIMA (Instituto Nacional de Vigilancia de Medicamentos y Alimentos) had denounced this product as fraudulent and illegal.

After 11 days of hospitalization with no improvement of liver chemistry and persistent jaundice, the patient presented an elevated INR, categorizing the hepatotoxicity as severe DILI. However, no accompanying neurological changes were observed, indicating the absence of acute liver failure. Therefore, a liver biopsy was performed to elucidate the cause of his acute hepatitis and determine the appropriate therapeutic approach.
The biopsy result showed changes compatible with acute hepatitis and a mixed inflammatory infiltrate with lobular lesion pattern, which could indicate DILI (figure 4). Considering the duration of symptoms and the possibility of idiosyncratic mechanisms of injury, a therapeutic trial with oral prednisolone was initiated, based on the assumption of immune-mediated injury. A final Roussel Uclaf Causality Assessment Method (RUCAM) score of 7 (probable) was calculated. After initiation of treatment he showed clinical improvement and resolution of his condition, leading to discharge. During outpatient follow-up the patient made a full recovery and received education on the risks of ingesting unapproved herbal substances, especially when the true ingredients were unknown.

Discussion

In the case presented, hepatotoxicity is related to the consumption of an over-the-counter "natural" remedy intended to control recurrent nephrolithiasis. A thorough examination, including patient history, physical evaluation, laboratory tests, and liver biopsy, consistently ruled out several potential causes of hepatitis and liver function abnormalities. Drugs have many different mechanisms and actions that damage the liver, and even after liver biopsy, if DILI is suspected, differential causes should be...
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Figura 4. Pathological findings of the biopsy performed. Sections A and B show the hepatic parenchyma with little representation of the portal spaces, a severe alteration of the hepatic architecture and a mixed portal and lobular inflammatory infiltrate, in which mostly lymphocytes, some plasmacytes, neutrophils and eosinophils are recognized, a ballonized degeneration of hepatocytes, vacuolization of hepatocyte cytoplasm, reactive regenerative changes and the presence of apoptotic and necrotic hepatocytes.

ruled out [5]. These evaluations included investigations of viral agents, autoimmune diseases, cholelithiasis, storage disorders, and endocrine conditions [5,6]. Particularly noteworthy is the temporal correlation between patient use of “stone-breaking wine (chancapiedra),” purportedly containing Phyllanthus niruri, and the occurrence of hepatotoxicity. This strong temporal association clearly indicated that the herbal supplement was the likely causative agent, although the substance was not tested since the patient no longer had it. This case underscores the importance of recognizing alternative remedies as potential hepatotoxic substances, and emphasizes the need for increased surveillance and evaluation of such products in clinical settings. We searched the MEDLINE and LILACS databases and found no other cases of DILI secondary to this agent.

To gain a comprehensive understanding of the scope and implications of DILI and HILI it is essential to explore the epidemiological aspects of these conditions. Global and local registries play a critical role in monitoring the safety of drugs and herbal products in the context of human health. Some of the most crucial epidemiological insights have emerged from regions such as the United States [7], Spain [8], China [9], India, and Latin America [10]. It should be noted that all these registries are prospective, except for China, which is retrospective. Notably, in India, China and Latin America, antituberculosis drugs are among the top three causative agents, and herbal substances are notable contributors to the respective registries in all countries [7-10]. In addition, the product Herbalife® is consistently described in the registries of Latin America, Spain and the United States [10].

Although the substance labeled as chancapiedra is supposed to be Phyllanthus niruri, used especially in India and Brazil, it has paradoxically long been reported as an antihepatotoxic agent [11]. Phyllanthus niruri, a member of the family Euphorbiaceae, is native to tropical regions and has a rich history in traditional medicine [12,13]. Known as chancapiedra in most Latin American countries, quebra-pedra in Brazil and bhumyamalaki in India, this plant is associated with various health benefits [12]. It is believed to act by interfering with reactive...
oxygen species (ROS)-induced apoptosis, enhancing lipid peroxidation [13]. In addition, antiurolithiatic, antidiabetic, hypolipidemic, anti-inflammatory and antiviral properties are attributed to it, especially against HIV and hepatitis B [12]. While most animal studies, including toxicity evaluations in rats, have reported no adverse effects or significant changes in laboratory values or liver biopsy results [14], limited human clinical trials have not demonstrated significant benefits in patients with chronic hepatitis B and alcoholic hepatitis compared to placebo [15,16]; however, a meta-analysis revealed some positive evidence for this intervention in nephrolithiasis, as was the reason for its use by the patient in this clinical case [17]. Although the Colombian health authority INVIMA issued an alert about fraudulent sales of the described product [18], the one used by the patient was not analyzed to evaluate its real components, or even if it was adulterated with other substances.

Drug- and herb-induced hepatotoxicity is often assessed by Hy’s law, which involves elevation of AST or ALT levels to 3 times the upper limit of normal (ULN), along with a total bilirubin level exceeding 2 times the ULN, in the absence of a cholestatic pattern or any other explanation other than drug exposure [5]. This criterion was first proposed by Zimmerman, who is considered the pioneer and father of hepatotoxicity research [19]. Substances that induce hepatocellular pattern injury that meet these criteria are associated with a 10% to 50% probability of causing acute liver failure [19].

There are mainly three mechanisms through which drugs can induce liver damage. The first mechanism is direct or intrinsic, characterized by dose dependence and predictability, and usually manifests within a few days of administration, as seen in acetaminophen toxicity. The second mechanism is indirect, in which the drug influences the immune system, leading to liver injury that can develop over several months, such as reactivation of hepatitis B after rituximab treatment. Finally, there is idiosyncratic injury, which is dose-independent, more host-dependent, unpredictable, and can develop from days to years after exposure, involving both metabolic and immunologic damage [1,6,20].

Further investigation into the role of corticosteroids and a comprehensive understanding of their efficacy in the context of the presenting patient’s condition are potential topics for future research. In particular, reputable guideline associations such as the AASLD (American Association for the Study of Liver Diseases) and its counterpart in Europe, the EASL (European Association for the Study of the Liver), commonly recommend corticosteroids based on several factors, including immune-mediated hypersensitivity, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome, autoimmune features observed in liver biopsies, associations with immunotherapy drugs and an INR >1.5, or in cases of drug-induced autoimmune hepatitis (DIAIH) [1,20]. It is crucial to emphasize these immune-mediated associations, as they often exhibit a rapid response to steroid treatment, as demonstrated in the case presented here. And if we return to our patient, the absence of clinical signs of hypersensitivity and its absence in the liver biopsy is striking. In addition, antibody tests were negative; however, the patient showed a clear improvement with the use of corticosteroids and there were no relapses after normalization of liver tests. All these findings suggest DILI with autoimmune features. The absence of relapses reduces the likelihood of drug-induced seronegative autoimmune hepatitis; however, the patient will continue to be followed long-term due to the prolonged latency of these clinical entities.
Conclusions

DILI and HILI are a rapidly growing concern today, especially in Latin America. It is probably associated with the increased use of over-the-counter medications and the indiscriminate use of herbal products without adequate safety studies, even for several common conditions, as seen in this case with renal lithiasis. Another challenge is its complex diagnosis and broad differential diagnosis, the lack of specific biomarkers and its similarity with other liver pathologies, which generates delays in diagnostic and therapeutic approaches. It was considered important to report this case, since there are no other published reports of hepatotoxicity due to *Phyllanthus niruri* (*chancapiedra*), and this product is available for purchase in Colombia. It is important to highlight that there was an alert from the Colombian drug regulatory service, INVIMA, about this substance. In this case, a temporal relationship was identified between the worsening of liver function and the initiation of the substance and its subsequent normalization after its withdrawal, associated with the use of corticoids. The response to corticosteroids is remarkable despite the absence of signs of hypersensitivity or positive antibodies, which suggests that this substance may be related to drug-induced liver damage with autoimmune characteristics. The seriousness of this case reminds us of the need to increase monitoring by drug regulatory authorities, implement educational campaigns for patients and inform the community about products with active alerts.

Data confidentiality

The project complies with Colombian Resolution 8430 of October 4, 1993, had the patient’s verbal and written consent for publication and the approval of the Research Committee of the Hospital Universidad del Norte. The authors declare that the procedures were followed in accordance with the standards established by the Ethics and Clinical Research Committee and with the Declaration of Helsinki of the World Medical Association, updated in 2013.

References


