Herbal therapy-induced toxic hepatitis – a case report

Rita Nortadas, José Barata

Abstract

A case of herbal therapy-induced toxic hepatitis is reported. Pathogenic mechanisms of hepatotoxicity of herbal products are discussed and causal nexuses are analysed. The goal of this presentation is to alert to the risk of severe adverse events while consuming false harmless products.

Key words: toxic hepatitis; alternative therapy..

INTRODUCTION

The consumption of products of botanical origin for therapeutic purposes has increased tremendously in industrialized countries in recent decades.[1]

The belief that natural products are harmless is strongly rooted in society, a conviction that is reinforced by the fact that they are easy to obtain and prescription-free, and the lack of reports of their potential harmless effects in the relevant literature.[1]

Adverse events induced by herbal medicines, although common, are still not well-known, and their pathogenic mechanisms have not been sufficiently investigated.[2] Cases of hepatotoxicity, the most well-documented and widely-studied adverse effect, have increased in recent years, in direct proportion to the increased consumption of these types of products.[1,2,3]

Since there are no specific markers, the diagnosis is arrived at by ruling out other possibilities, based electively on causal nexuses.[2] Clinical suspicion is essential, and today, the importance of research on consumer habits in relation to non-conventional drugs is considered an important part of the anamnestic enquiry.[2]

CASE REPORT

Male patient, aged 35 years, a businessman in the construction industry, married, born in Barreiro and resident in the county of Seixal.

Medical Service of the Hospital Garcia de Orta

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He came to the Medical clinic with asthenia, nausea, choluria, hypocholia and generalized itching, with progressive evolution. He denied other complaints, notably, arthralgia, fever, or alterations in the bowel movement.

He also reported that around two months previously, he had used alternative medicines to control obesity, having begun therapy with natural products, in the form of capsules containing Cascara buckthorn (*Rhamnus purshiana*) 50 mg, *Fucus vesiculosus* 100 mg, *Garcinia cambogia* 270 mg, *Camellia* (*Camellia sinensis)* 420 mg, Boldo (*Peumus boldus*) 50 mg, Chromium Polynicotinate 0.1 mg, Diazepam 3 mg, Chlordiazepoxide 3 mg, Cyclobutane methanamine 5mg, Bumetanide 0.3 mg, Potassium bicarbonate 175 mg and Vitamin A, treatment which he took continuously until the appearance of the described symptoms.

The personal history included a diagnosis of peptic esophagitis around 10 years previously, which was regularly medicated with Omeprazol, a therapy that was continued during the evolution of the symptoms.

He reported being a smoker 40 packs year, but did not have alcohol drinking or drug abuse habits.

He had no history of chronic or hereditary diseases, including diabetes mellitus.

The family history showed nothing of relevance.

On objective examination, the patient was obese (BMI 35), alert, collaborative, oriented and without fever.

Flagrant jaundice coloration of the skin and mucosa was observed.

Cardiopulmonary exam did not show any alteration.

The abdomen presented exuberant adipose paniculum, and non-complicated umbilical hernia. No

collateral venous circulation was evident.

No enlargement in liver or spleen volume were apparent on palpation, and there were no signs of ascites.

Palpation showed no adenomegalies in the elective sites, and there were no signs of hemorrhagic discrasia or portal-systemic encephalopathy.

There were no edemas of the lower limbs.

Neurological examination did not show any alterations, particularly in relation to muscle strength, sensitivity, and motor coordination.

Analytical results were as follows:

Hemoglobin 16.2 g/L; Platelets 228,000; leukocytes 7,900 (Neutrophils 55.7 % Lymphocytes 31.5 %; Eosinophils 1.3 %). ESR 2 mm on the 1st hour

Prothrombin Time 68 % ; aPTT 1.22 s. AST 1379 UI/L ; ALT 3281 UI/L; GGT 246 UI/L; Phosphatase Alkaline 228 U/L; Total Bilirubin 7.2 mg/dL; Direct Bilirubin 6.72 mg/dL.

Total Proteins 7.4 g/dL; albumin 57.6 % (4.26 g/dL). Electrophoretic pattern unaltered.

Renal function, ionogram and the remaining biochemical parameters were within the normal limits.

Ferritin, ceruloplasmin and alfa1-anti-tripsin levels were also within the normal range.

The hepatitis A, B, C, Cytomegalovirus and Epstein-Barr serologies and the VDRL were all negative.

The Anti-nuclear, Anti-mitochondria, Anti-smooth muscle, Anti-DNA and Anti-KLM antibodies were also negative.

Hepatobiliary echography showed liver with normal dimensions, distended, with regulation contours, without evidence of focal lesions. Portal and supra-hepatic veins permeable. Absence of dilation of the intra- and extra-hepatic bile ducts, or lithiasis.

Hepatic biopsy was not carried out given the stability and good evolution of the clinical symptoms.

The patient was immediately told to stop taking the herbal products, and was medicated with Domperidone and Cholestyramine. The evolution was characterized by progressive clinical and laboratory improvement, with sudden regression of the alterations in hepatic enzymology and bilirubin values, which normalized six weeks after suspending the ingestion of the products.

DISCUSSION

Bearing in mind that three of the botanical species used as constituents in manipulated drugs consumed by the patient are involved in cases of hepatic lesion (Camellia sinensis, Peumus boldus and Rhamnus purshiana), a diagnosis of toxic hepatic diagnosis was made, caused by substances of botanical origin used for therapeutic purposes. The temporal correlation between exposure and inhalation of the clinical-laboratory symptoms, the exclusion of other potentially hepatotoxic factors, particularly those of chemical, infectious or metabolic etiology, and the regression of the symptoms after suspending the drug, consistently support this diagnostic hypothesis.

The CIOMS/RUCAM clinical scale for evaluating causality for toxic hepatitis gave a score of 6 for the present case, indicating a probable causal relation. The Maria & Vitorino scale, which has less power of discrimination but is easier to apply, gave a score of 11, compatible with a possible causal nexus.

The hepatotoxicity related to the consumption of the herbal products in the scope of alternative medicines has been widely documented in the scientific literature, particularly since the last decade of the last century. Around forty botanical species used for therapeutic purposes are identified, whether in their natural state or in the form of manipulated drugs, which are liable to induce hepatic toxicity of varying intensities, commonly evolving to acute hepatic insufficiency requiring transplant.[1,2,3]

Hepatic toxicity by *Camellia sinensis* was notified for the first time in Europe in 1999, and from that time until the end of 2008, thirty-six cases have been identified, mainly in Spain, France, Italy and Great Britain.[4,5]

The pathogenic mechanisms of hepatic aggression caused by this botanical species have provoked much debate. Green tea, an infusion of the leaves of *Camellia sinensis*, is a social drink that is widely consumed worldwide, and is considered harmless from the point of view of toxicity. However, products marked for therapeutic purposes, particularly some hydroalcoholic drugs, have demonstrated high hepatotoxic effect. This fact led the pharmacosurveillance authorities in France, Spain and Italy to ban the commercialization of these products in 2003.[2] But they are still available on the manipulated products market, obtained by aqueous extraction, for which toxicity has also been proven.[4]

Hepatotoxic reactions by extracts of *Camellia sinensis* do not present a uniform pattern in the different series of case studies. The majority of occurrences are

type B (idiosyncratic), with long dormant periods and no relation to the dosage consumed;[2,4,5] In a smaller number of cases they are type A (direct toxicity), with earlier onset and various documented episodes of clinical-laboratory recurrence after re-exposure.[4,6]

The variability of the toxic effects of the different preparations of *Camellia sinensis* appears to be related to the methods used in its preparation.[4,5]

In the chemical composition of the leaves of the plant, polyphenolic compounds are prevalent, namely catechin. Of these, the most significant one, in quantitative terms and in relation to pharmacoactivity, is epigallocatechin gallate (EGCG).[2,4,5] Despite the lack of conclusive data, the toxic effect of catechins appears to be mediated by EGCG,[4,6] which reaches variable concentrations in the final product, according to the preparation processes used. The methodology used in the production of phytotherapeutic products from *Camellia sinensis*, which generally involves crushing the leaves, significantly increases the EGCG content of the final product, reaching maximum concentrations with the use of hydroalcoholic excipients.[4,5] Immersing the leaves in boiling water for a period of time - the universal method of preparing conventional green tea – significantly decreases the release of EGCG, preventing it from reaching toxic levels.[5]

The majority of described cases of hepatotoxicity by *Camellia sinensis* occurred with the use of weight-loss therapies, and were characterized by mixed symptoms, with intense cytolysis and a marked cholestatic component.[2,4,6,7,8] The clinical evolution was generally favorable, with the exception of three cases of fulminant evolution, one of which was fatal.[4,5] The time interval from taking the remedy to the onset of symptoms ranged from 1 week to 3 months, and around 2 months were needed to completely normalize the hepatic enzymology, after discontinuing the exposure.[4,5]

Another two species consumed concomitantly by the patient are also associated with hepatic toxicity: One case of cholestatic hepatitis by *Peumus boldus* is described, and another by *Rhamnus purshiana,* both evolving spontaneously to cure, around three months after suspension of the exposure to the product.9,10 Phenolic compounds are prevalent in the chemical composition of Peumus boldus, therefore the toxicity mechanism may be identical to those described for Camellia sinensis.9 The toxicity of Cascara buckthorn *(Rhamnus purshiana)* will probably be measured by anthraquinone compounds, by indeterminate mechanisms.10

Chromium picolinate is a supplement that is commonly used in alternative medicines, in association with herbal products, for weight-loss therapies. Two cases of multiorgan toxicity by this oligoelement are documented, involving hemolysis, thrombocytopenia, renal insufficiency and hepatic dysfunction.11 A third published case attributes chromium salts to the etiology of a condition of toxic hepatitis, in a patient who had simultaneously consumed a species of *Rhamnus purshiana.*[11] Therefore, there is no conclusive evidence of exclusive hepatotoxicity associated with this product.

Also, there is no documented evidence in the literature, of hepatic adverse effects attributable to the species *Garcinia cambogia* and *Fucus vesiculosos*, or to the drugs Diazepam, Chlordiazepoxide, Cyclobutylmethanamine and Bumetanide.

Although two cases of toxic hepatitis by Omeprazol have been described,[12] this drug was not considered as an etiological hypothesis, given the time of evolution of the previous drug (around 10 years) and in view of the favorable evolution of the symptoms, even though the patient did not suspend its use.

The problem of safety of natural products proposed by alternative medicines has not been given adequate legal consideration by the health regulatory agencies. Since they are marketed as food supplements, and not medications, they are exempt from the complex certification process required of synthesis drugs. Their availability in non-specialized stores, their ease of acquisition, the fact that they do not require a prescription, and the high offer available in the Internet, are important factors behind the intense growth in consumption seen in developed countries.

The fact that they are natural, as consumers are led to believe, does not mean products of botanical origin are safe; the fact that they contain molecules with potential pharmacoactivity does not mean these products effective are drugs; and the fact that they are traditionally used, for therapeutic purposes, does not give them legitimacy as medications of election, far less as harmless substances.

Any product for therapeutic use, whether of natural or synthetic origin, must demonstrate that it is safe and effective, and this safety and efficacy must be proven through reliable clinical trials.

The risks associated with the consumption of

uncertified products that circulate on the periphery of the pharmacosurveillance regulations constitute a growing problem that requires an attentive attitude on the part of clinicians, particularly with regard to the undesirable effects. ■

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