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CASE REPORT

Aloe vera-induced acute liver injury: A case report and literature review

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Summary Recent data suggest that herbal and dietary supplements are the second most common cause of liver injury. We herein report a case of acute liver injury in a 68-year old female caused by ingestion of Aloe vera. Upon discontinuation of the oral Aloe vera, liver function tests (LFT) returned to normal levels. Thus, it is crucial to consider the use of herbal products as causative agents of acute liver injury.

Introduction

The worldwide use of medicinal herbs has increased over the past years owing to their affordability and their presumably reduced side effects when compared to the traditional drugs. However hepatic toxicity due to herbal agents was described in the medical literature, revealing sixty-five different commonly used herbs, herbal drugs and supplements which could cause liver diseases [1].

Drug- and herb-induced liver injury (DILI and HILI, respectively) continue to raise interest, as suggested by the increasing number of publications indexed in PubMed [2]. DILI is the fourth leading cause of hepatic damage and the leading cause of acute liver failure (50% of cases, including acetaminophen) in industrialized countries, with an incidence rate of 34.2 ± 10.7 cases per 10^6 inhabitants in a Spanish study [3] and 13.9 ± 9 cases per 10^6 inhabitants in a French study [4].

In the case of HILI, the absence of regulatory surveillance compromises the accuracy of reported incidence. A recent tabular compilation of published case reports of HILI found a causality ''likely'' or ''probable'' in 28 out of 57 identified herbal products [2]. Furthermore, a recent study in the United States estimates that 15% of DILI are caused by herbs

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[5]. A study from the Drug-Induced Liver Injury Network (DILIN) identified herbal and dietary supplements (HDS) as the second most common cause of liver injury [6], making the actual safety and benefits of HDS questionable [7,8].

Aloe vera has gained popularity over the past decade, owing to its potential antitumor, antioxidant, anti-inflammatory, antiarthritic, antirheumatic, anticancer, antidiabetic and hepatoprotective properties [9]. For example, it has been recommended to treat constipation, gastrointestinal disorder and immune system deficiency [9]. Additionally, Aloe vera is commonly used as a self-prescribed anti-aging agent. However, its toxicology is not well known. We herein report a case of Aloe vera-induced liver injury, including also a brief literature review in the field.

Case report

A 68-year old Burkinabe female patient presented to our department in May 2015 with acute liver injury. The patient was asymptomatic and had blood tests performed as part of the routine checks. Past medical history revealed non-insulin dependent diabetes mellitus treated with metformin, high blood pressure treated with valsartan, and dyslipidemia treated with rosuvastatin. Her medical history did not reveal any preexisting liver disease, and the LFT were within normal limits. Past family medical history was unremarkable. There was no history of illicit drug and alcohol use, no sexual promiscuity and there was no mention of foreign travel. The patient had not taken new drugs in the last period. However, she admitted she had been taking Aloe vera pills for the past several months. Clinical examination revealed a mild overweight (BMI 26.9 kg/m^2), normal liver and spleen size, no right upper quadrant tenderness, no jaundice. There was no sign of chronic liver disease. The rest of the physical examination was unremarkable.

Laboratory studies revealed: ALT 196 IU/L [upper limit of normal (ULN) = 35 IU/L], AST 179 IU/L (ULN = 35 IU/L), GGT 196 IU/L (ULN = 36 IU/L). Renal function, serum electrolytes, lipids, glycated hemoglobin, CPK, electrophoresis, hemoglobin concentration, platelet count, white blood cell and different blood cell counts were normal. There was a mild hypothyroidism (TSH 7.17 μIU/mL, normal < 4.2).

Serologic examinations for acute viral hepatitis (A, B, C, E) were negative. Anti HBc-IgG and anti-HBs-IgG were positive, while HBs-Ag was negative. Anti-HAV IgG was positive, while anti-HAV IgM and anti-HCV were negative. Autoimmune hepatitis, Budd-Chiari syndrome and portal vein thrombosis were ruled out by appropriate immunological and imaging methods. Abdominal ultrasonography was normal and transient elastography showed an average elasticity of 4.7 kPa (IQR 0.5 kPa, SR 100%). Upon discontinuation of the oral Aloe vera, LFT returned to normal levels within 51 days: ALT 17 IU/L, AST 17 IU/L, GGT 43 IU/L.

Discussion

The causal relationship between Aloe vera use and DILI was evaluated using the Roussel Uclaf Causality Assessment Method (RUCAM) scale [10], which includes several criteria such as: temporal relationship between drug intake and development of abnormal LFT, evolution of LFT following drug withdrawal, alcohol consumption, age, previous case reports of DILI, concomitant medication, exclusion of all potential causes of liver damage, drug rechallenge. In our patient, causality of Aloe vera was evaluated as ''probable''. The patient had not taken any new medicines and the suspension of the Aloe vera has resulted in a rapid normalization of LFT. As this treatment was taken in Africa and derived from plants, it is unfortunately impossible to precisely know the purity and the dose. Nevertheless, idiosyncratic DILI or HILI is typically not dose related.

It is unlikely that concomitant treatment with statins has been the cause of liver injury, as this treatment was maintained whereas liver enzymes level improved.

There is evidence in the literature on Aloe vera as the causative agent of toxic acute hepatitis. R ratio [R = (ALT value ÷ ALT ULN) ÷ (Alk P value ÷ Alk P ULN)] cannot be calculated due to the lack of alkaline phosphatase data at the time of acute injury diagnosis [11]. However, one can assume a hepatocellular damage as indicated by the indices of cytolysis and cholestasis in subsequent blood tests determinations. Bilirubin levels and blood clotting tests were not initially performed, but jaundice and other signs of liver failure were absent at physical examination. Furthermore, LFT rapidly improved upon Aloe vera withdrawal. Liver injury is therefore unlikely to be severe.

Few cases of liver injury related to Aloe vera are reported in the literature [12—17]. Clinical, biochemical and liver histology features of these cases are shown in Table 1. In the different case reports, patients ranged from 24 to 73 years of age. There were 7 female and 2 male patients. The main reasons for intake of Aloe vera were anti-aging, ''healthier living'' purpose, constipation and weight reduction. The daily dose of Aloe vera is variable in the different case studies, as well as the latency period. More frequently, patients were hospitalized for general malaise, fatigue, jaundice, pruritus, upper abdominal discomfort, mild nausea and vomiting. Bottemberg et al. report a 73-year-old female patient with poor appetite, a weight loss of approximately 1.8 kg and a rash that had developed on her back 2 weeks before the onset of acute illness. In our case, the patient was asymptomatic probably due to the fact that, having run routine blood tests, she benefited from preclinical diagnosis of liver injury. The type of liver injury, determined through the R ratio, was hepatocellular injury in the totality of the cases described. In our case, due to the unknown level of alkaline phosphatase, we could not calculate the R score, but considering the rapid remission of liver damage upon Aloe vera discontinuation, we could assume a hepatocellular type of liver injury. In another case, transient leucopenia and thrombocytopenia were associated with liver enzyme increase [15]. Positive autoimmune marker (ASMA 1:160) was present in another case, but liver pathology and autoimmune panel score were not consistent with the diagnosis of autoimmune hepatitis [12]. The RUCAM [10] score was probable in six patients and definite in 2 patients. In one case, a patient started taking the same Aloe extract again 1 month after being discharge from hospital, and the rechallenge was positive [16]. Liver biopsy was performed in 6 patients and it mainly revealed portal and acinar inflammatory cell infiltration (neutrophil, eosinophilic and monocytes) with bridging necrosis and bile stasis.