Aloe vera Induce Acute Liver Injury and Chronic Liver Disease: Case Report

Abou Rached Antoine¹*, Al Alam Farid¹, Zaiter Aline¹ and Joyce Sanyour²

¹School of medicine, Lebanese University, Beirut, Lebanon,
²Sultan Qaboos Comprehensive cancer center, Muscat, Oman

Abstract

Herbal induced liver injury is increasing, usual spontaneous resolution is noted in the majority of cases but few cases were reported to had chronic liver disease and required liver transplantation. Aloe vera, an herbal supplement, is known to induced hepatitis, typically self-limited once the herb is stopped. We reported the first case with acute hepatic injury due to Aloe Vera associated with nephrotoxicity and chronic hepatic injury.

Keywords:
- Aloe vera
- Liver Injury
- Herbal Supplement
- Nephrotoxicity
- Macular Skin Rash
- Liver Biopsy

Introduction

Dietary supplements cause an estimated 23000 emergency department visits in the united states every year, herbal products were commonly implicated [1].

While there have been well documented outbreaks of acute liver injury associated with specific dietary supplements, the incidence of herbal induced liver injury (HILI) is difficult to estimate but their reporting is increasing due to growing awareness of the potential hepatotoxicity for these agents [2]. In most cases, the injury is mainly hepatocellular, but cases with small bile ducts loss have been reported [3]. Despite the usual spontaneous HILI resolution after agent discontinuation, the course may be much less favourable in others in which liver transplantation may be required and death may occur. A specific herbal supplement, Aloe vera, extract of the Aloe
Abourached Antoine, et al., 2023

barbadensis miller plant, is known for its potential antitumor, antioxidant, anti-inflammatory, antiarthritic, antirheumatic, anticancer, antidiabetic, hepatoprotective and laxative properties [4]. However, its potential harmful effect is not well studied.

We report the first clinical case describing a concomitant acute hepatitis, nephrotoxicity and chronic liver disease, all associated with Aloe vera ingestion.

**Case Report**

47 year female patient presented to gastroenterology department for 3 days history of fatigue and jaundice. Past medical history did not reveal any pre-existing liver disease. There was no history of illicit drug use, no alcohol consumption, no history of blood transfusion, no travel history and no sexual promiscuity.

On clinical examination she is afebrile and hemodynamically stable, without neurological changes. She was jaundiced with aphthous oral lesions. Abdomen was soft without hepatomegaly or splenomegaly. There was no lymphadenopathy. During Hospitalization, the patient developed macular skin rash (Figure 1).

**Figure 1:** Maculopapular Rash

On admission, abdominal ultrasound examination showed mild hepatomegaly with absence of dilatation of intra- or extra hepatic bile ducts. Patency of the hepatic artery, portal vein, and hepatic veins was ascertained using Doppler ultrasound. Splenic size was normal, the examination of kidneys, pancreas and retroperitoneal space was normal as well.

**Results and Discussion**

Laboratory abnormalities included increase liver enzyme with ALT 715 IU/L (Normal <30 IU/L), Alkaline phosphatase of 394 IU/L (NL<120IU/L), GGTP 500 IU/L (NL <60 IU/L), total bilirubin 21.2 mg/dl (NL<1.2mg/dl) with direct bilirubin of 11.4 mg/dl (Figure 2). LDH and CRP were 394 IU/L (NL<240 IU/L) and 10 mg/dl (NL<6 mg/dl) respectively with very high ferritin level 2648 mcg/l (NL<200mcg/L). White blood cell count and differential, hemoglobin concentration, platelet count, Creatinine, serum electrolytes, amylase, protein electrophoresis, serum concentrations of IgG, IgA, and IgM and Iron were all within the normal range. Ceruloplasmin concentration was normal as was the alpha-1-antitrypsin concentration. Hepatitis serology of A, B, C, E were negative.

Autoimmune work up showed negative titers. Herpes serology showed IgM: 110 (Pos > 20Ru/ml) and IgG: 2.6 (Pos >1 Ru/ml). PCR Herpes Simplex Virus was negative liver biopsy done and show a preservation of hepatic architecture, infiltration of portal space by leucocyte, micro and macro nodular steatosis, perivenular fibrosis with Masson stain and preservation of reticuline tram (Figure 3). Two days after hospitalization she start to increase her cholestatic pattern Asking her again about new medication or herbal used, she notices the use of DETOX of Aloe Vera 20 days previous to presentation. Based on Rousell Uclaf Causality Assessment Method (RUCAM) her score was 8 which goes with high probable case of HILI on Day 9 of hospitalization, the liver function test start to decrease and the patient discharge home with follow up liver test.
Three weeks later, she returned to the emergency department with severe jaundice, fatigue, nausea, anorexia and vomiting, and the labs showed hyponatremia, hypokalemia, acidosis, hypophosphatemia, hypoalbuminemia and hypocalcemia with severe increase in cholestatic patterns (total Bilirubin: 62, direct bilirubin:23, Alkaline phosphatase: 800, gamma GT: 900. ALT: 156) (Figure 2). In addition to hepatic injury due to Aloe Vera our patient developed Nephrotoxicity (immune allergic interstitial nephropathy). Magnetic resonance cholangiopancreatography to rule out Primary Sclerosing Cholangitis was normal. Prednisolone was started as treatment of kidney and liver injury induced by herbal and progressively the liver function test started to decrease. After stopping the steroid and during a period of 3 months, the patient continue to have abnormal liver function test mainly cholestatic (Figure 2).
A new liver biopsy was done (Figure 4) showing a mild centrilobular steatosis and fibrosis, presence of Councilman body, leucocyte infiltration of the portal space with fibrosis. The patient probably developed a vanishing bile duct syndrome with long term persistent cholestatic injury. Ursodeoxycholic acid started at 15mg/kg. Follow up during a period of 2 years show normalization of bilirubin but ALT and ALP still elevated around 2 and 3 ULN (Figure 2).

Discussion

Hepatotoxicity from herbal medications is an under recognized problem. Patients usually take herbal supplementation with assumption that it is safe. Without careful history taking, many patients won't admit to using herbal supplementation. There are two proposed pathogeneses of herbal induced liver injury (HILI): direct toxicity and idiosyncratic mechanism [5,6].

In most cases, the injury is mainly hepatocellular but cases with small bile duct loss have been reported. Spontaneous resolution within weeks usually occurs after herb discontinuation. However, the course may be much less favourable in other HILI in which liver transplantation may be required and death may occur and the development of chronic liver disease was reported only in 1.5% of cases [7–11]. The development of chronic liver disease was reported only in 1.5% of cases 12. In severe cases, death occurred only a few days after hospitalization due to fulminant liver failure [10,13].

Aloe vera, chemically ill-defined extract of the Aloe barbadensis miller plant, is known to contain several superoxide dismutase enzymes in addition to possessing peroxidase activity. It is also thought to have antioxidant and immune-modulator effects [14,15]. Because of these attributes, investigators have examined use of aloe vera in several inflammatory disease states, including ulcerative colitis [16]. Aloe Vera contains also several alkaloids that may induce or block hepatic enzyme systems such as cytochrome P450 as well as the enzymes of ethanol metabolism which may lead to dose-related liver damage or direct cytotoxic effects of Aloe or bio transformed constituents. In Addition, Hypersensitivity to aloe has been described in humans. Also, several reports have revealed Aloe vera induced toxic hepatitis and severe liver injuries [8–10,17–21].

Figure 4: Second liver biopsy (a- fibrosis and leucocyte infiltration of portal space, b- Councilman body, c- Centrol lobular steatosis, d- Mild steatosis and fibrosis, e- Reticuline collapse).
In published case of aloe vera induce hepatitis, the mean age is 50 years with higher prevalence in women (77.3%). The main symptoms include abdominal pain, jaundice, fatigue, and nausea. The injury typically arises between 3 weeks to 24 weeks after starting oral aloe vera. Hepatocellular was the most common pattern of lesion. Rare cases of liver injury reported with aloe vera use have had idiosyncratic features [22–24]. Normally, it is typically self-limited once the herb is stopped. A poor prognosis was normally associated with the consumption of multiple herbs and resulted in liver transplantation and death. Normalization of LFT occur within 4–6 months with decrease of ALT level > 50% from peak within 8-30 days [22,25–30].

Concerning the nephrotoxicity of Aloe Vera, to our knowledge it’s the first clinical cases reported. But it’s well known that in rats, the highest accumulation of aloin in kidney, results in nephrotoxicity [31]. A decrease in glomerular cellularity was observed with shrunk glomeruli which may be due to the presence of several phytochemicals in Aloe vera [32,33]. Aloe vera treated mice also experienced urinary space dilation in renal corpuscle leading to urine assemblage in urinary space and decreased glomerular filtration rate. Also, regular intake of Aloe vera at a relatively low dose resulted in several histopathological alterations in mice renal tissue suggesting further research to examine the safety of aloe preparations as a food additive [34,35].

The patient was considered as a case of Aloe vera induced hepatitis she had a RUCAM score of 8 which goes with high probable case of HILI. It’s well established that RUCAM is a diagnostic tool based on 7 clinical criteria and is the most widely used and accepted DILI [36–38]. She developed first hepatocellular injury with R ratio equal 9.1 she was considered to have moderate to severe hepatic injury based on US DILI network and severe hepatic injury based on international DILI expert working group [39]. Then she developed Cholestatic liver injury with nephrotoxicity (immune allergic interstitial nephropathy) treated with steroid with clinical and biological response. The EASL guidelines suggest the use of corticosteroid therapy in patients who do not show recovery despite drug cessation, with the intention of preventing progression of persistent liver injury [40]. Corticosteroids can also be used to treat drug-induced cholestatic hepatitis, in particular in DILI associated with hypersensitivity features such as eosinophilia, rash and fever. But there is no consensus concerning the use of steroids for treatment and management of chronic DILI/HILI in United States, Europe, Asia, and China [5,41–46].

According to EASL guidelines, persistent elevation of total bilirubin and ALP in the second month from HILI/DILI onset should be used as a marker for chronic DILI [40]. And liver biopsy can be considered in patient with suspected DILI progresses or fails to resolve on withdraw of the causal agent [40].

Our case is the first case of acute hepatitis due to aloe vera with nephrotoxicity and development of cholestatic liver disease with progression to chronic liver injury.

Conclusion

In Conclusion, due to the widespread use of herbal products and difficulty in determining patients’ use of such therapies, clinicians are faced with challenges in assessing what products patients are utilizing. In cases of acute hepatitis that is not readily diagnosed, clinicians should question patients specifically about herbal product use and should consider aloe vera as a possible cause.

Acknowledgements: All the authors equally contributed for entire manuscript.

Conflict of Interest: No potential conflict of interest was reported by all the authors. All authors agree to be accountable for all aspects of the work.

Ethical Approval: All the information has been granted by patient

References:

44. Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-Related Adverse Events (irAEs): Diagnosis,