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CASE REPORT

젊은 여성에서 알로에 베라 복용 후 발생한 독성간염 1예

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Acute Toxic Hepatitis Caused by an Aloe Vera Preparation in a Young Patient: A Case Report with a Literature Review

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Aloe is one of the leading products used in phytomedicine. Several cases of aloe-induced toxic hepatitis have been reported in recent years. However, its toxicology has not yet been systematically described in the literature. A 21-year-old female patient was admitted to our hospital with acute hepatitis after taking an aloe vera preparation for four weeks. Her history, clinical manifestation, laboratory findings, and histological findings all led to the diagnosis of aloe vera-induced toxic hepatitis. We report herein on a case of acute toxic hepatitis induced by aloe vera. **(Korean J Gastroenterol 2014;64:54-58)**

Key Words: Hepatitis; Aloe; Health food

INTRODUCTION

Use of functional health foods has increased worldwide.[1] Aloe accounts for a large proportion of the market for all functional health foods in Korea.[2] People view it and other such products as safe, but, according to recent research, aloe vera may cause toxic hepatitis. However, no systematic research on such possibility has been conducted. Accordingly, functional health foods like aloe vera should be considered possible causes of liver injury. To support such a possibility, we report herein on a case of toxic hepatitis induced by aloe vera.

CASE REPORT

The patient was a 21-year-old woman who presented to our hospital with several days' history of abdominal discomfort and nausea. At the time of her visit to our hospital, her height was 163 cm and her weight was 50 kg, with a body mass index of 18.82 kg/m^2. She presented to our department with a week's history of abdominal discomfort, nausea, and mild fever. Hoping to reduce weight, she had taken 30 mL aloe vera gel (extract powder 200 : 1, Herbalife®; Herbalife, Los Angeles, CA, USA) twice a day for approximately one month before her admission (Fig. 1). She was healthy, and her family history and past medical history were unremarkable. She was not prescribed any medication, and she did not consume alcohol.

She was medically stable with a blood pressure of 113/74 mmHg, a pulse of 75 beats per minute, a respiration rate of 20 breaths per minute, and a temperature of 38.1°C. Normal heart and breath sounds were observed upon her auscultation. There was no specific finding of abdominal ausculta-

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tion, but tenderness with mild splenomegaly was observed on her upper abdomen.

The patient's complete blood count showed a white blood cell (WBC) of 850/μL (segmented neutrophils 46.4%, lymphocytes 39.6%, eosinophil 0.1%), hemoglobin of 14.0 g/dL, hematocrit of 41.7%, and platelet count of 57,000/μL. The serum biochemical assay showed the following results: BUN, 7.5 mg/dL; creatinine, 0.8 mg/dL; Na, 141 mEq/L; K, 3.9 mEq/L; Cl, 105 mEq/L; albumin, 4.0 g/dL; AST/ALT, 2,449/1,703 IU/L; total bilirubin/direct bilirubin, 1.5/0.9 mg/dL; GGT, 249 IU/L; ALP, 709 IU/L; and LDH, 4,802 IU/L. The IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV, HCV real-time polymerase chain reaction, anti-HEV, and anti-HIV test results were all negative. However, the results of IgG anti-HAV and anti-HBs tests were positive. There was no serologic evidence of recent infection with cytomegalovirus, Epstein-Barr virus, or herpes simplex virus. All autoimmune markers were negative: anti-nuclear antibody (Ab), anti-mitochondrial Ab, anti-smooth muscle Ab, IgG sub 4, and anti-liver kidney microsomal Ab. The blood coagulation test showed a PTT of 29.8 seconds. The reticulocyte count was 0.6%. The ceruloplasmin concentration and the alpha-1-antitrypsin concentration were normal.

Fig. 1. The container bottle and gel of the aloe vera preparation that the patient had taken.

Abdominal computed tomography showed splenomegaly because the spleen was more than 13 cm long and hepatogenous enhancement of the liver parenchyme in the arterial phase, periportal lucency, gall bladder swelling, ascites in the pelvis, and splenomegaly. However, the intra- or extrahepatic bile ducts were not dilated.

A liver biopsy revealed portal and lobular infiltrates consisting of neutrophils, lymphocytes, and eosinophils. There was inflammatory cell infiltration in the hepatic lobule. There was no bile stasis, fatty change, or fibroplasia (Fig. 2).

The ALT was highest (2,297 IU/L) on the third day of admission and gradually decreased to 88 IU/L on the 14th day of admission (Fig. 3A). The abdominal discomfort and nausea improved from the fourth day of admission. The culture test results were negative. The ALT, ALP, and total bilirubin gradually returned to normal at 14 IU/L, 213 IU/L, and 0.8 mg/dL, respectively, on the 28th day, when the patient was discharged.

The time from drug intake to the reaction onset was four weeks (point: 2), and from drug withdrawal to the reaction onset, 15 days (point: 1). The ALT decreased by >50% from the

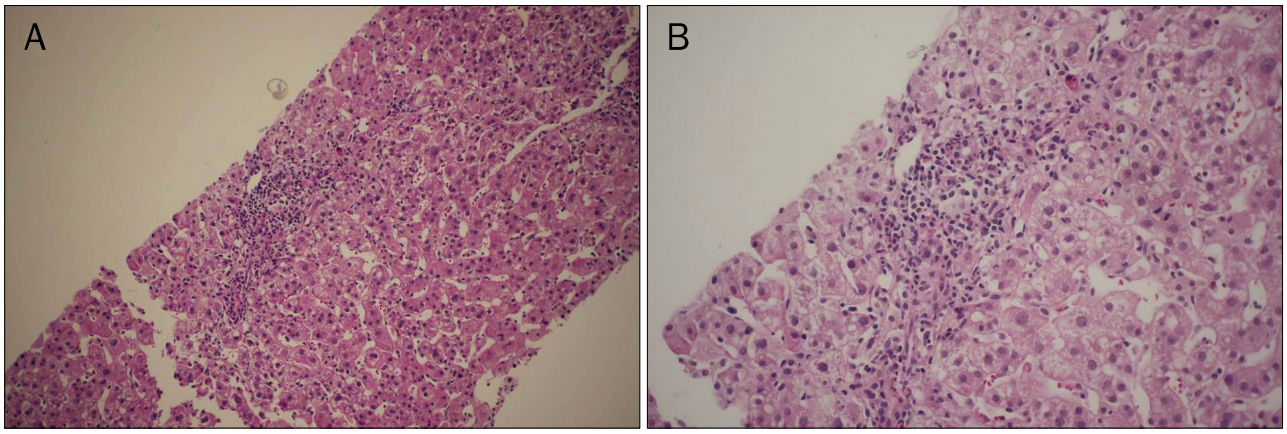

Fig. 2. (A) Microphotograph of a gun biopsy specimen of the liver (H&E, ×200). (B) Higher magnification showed mixed infiltration of inflammatory cells at the portal and lobular spaces with neutrophils, lymphocytes, and eosinophils (H&E, ×400).

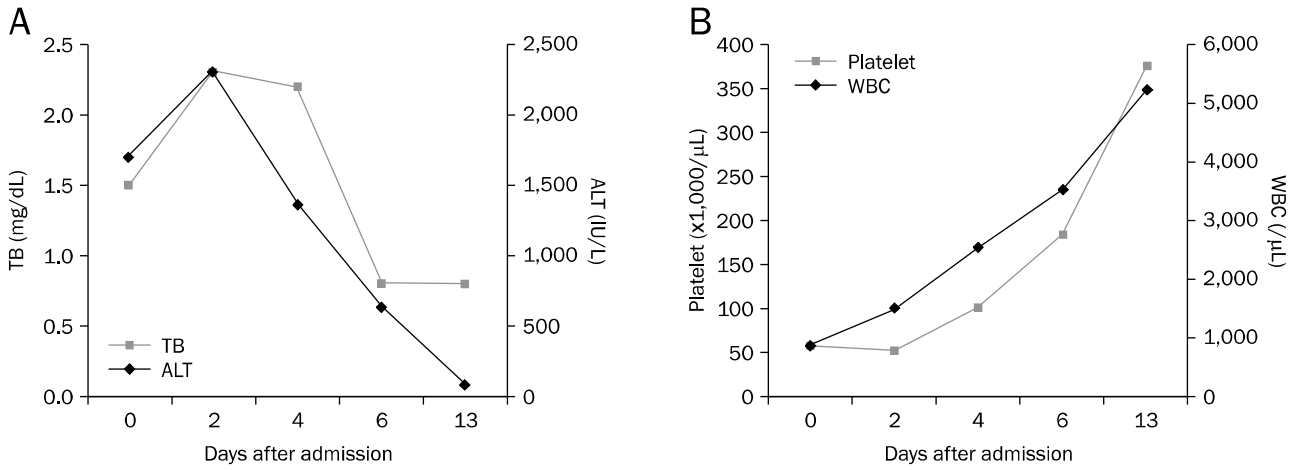

Fig. 3. (A) Upon discontinuation of the intake of aloe vera, the liver enzymes returned to their normal level. (B) Upon discontinuation of the intake of aloe vera, the white blood cell and platelet counts returned to their normal levels.
TB, total bilirubin; WBC, white blood cell.

Table 1. Patient Characteristics of Previously Reported Aloe-induced Toxic Hepatitis

Patient (No)	Sex	Age (yr)	Medication duration (wk)	ALT (IU/L)	ALP (IU/L)	TB (mg/dL)	Type of liver injury	Re-challenge	Causality assessment[a]
1[7]	F	57	4	1,480	256	8.90	Hepatocellular	ND	Probable
2[8]	F	57	24	565	309	1.07	Hepatocellular	ND	Probable
3[8]	F	62	12	1,564	211	14.64	Hepatocellular	Positive	Definite
4[8]	F	55	20	641	291	0.48	Hepatocellular	ND	Probable
5[9]	F	73	260	1,451	535	10.70	Hepatocellular	ND	Probable
6[10]	M	26	156	799	200	8	Hepatocellular	ND	Probable
7[11]	M	24	3	2,550	400	9.00	Hepatocellular	ND	Probable
Current case	F	21	4	1,703	709	1.5	Hepatocellular	ND	Definite

[a]The causality assessment according to the Roussel Uclaf Causality Assessment Method (RUCAM)/Council for International Organizations of Medical Sciences (CIMOS) criteria.
F, female; M, male; TB, total bilirubin; ND, not done.

peak within eight days (point: 3). Non-drug-related causes were all excluded (point: 2). Previous information on aloe-induced hepatitis was published in case reports but not on the package label (point: 1). Using the Roussel Uclaf Causality Assessment Method (RUCAM) scale,[3] the drug hepatotoxicity score was 9.

DISCUSSION

In 2011, the functional health foods world market accounted for about 200 billion USD while the domestic market accounted for about 4.7 billion USD. In the Korean market for functional health foods, aloe was top 4 in sales, ranking at 69.2 billion Korean won (63.7 million USD). In addition, its sales have been increasing each year.[2]

There are about 400 different kinds of aloes. Aloe vera is commonly used in phytomedicine. In general, aloe is regarded as a good agent against cancer and inflammation and for liver protection and immunity modulation. However, its safety and stability are caught up in a controversy.[4] Recently, people have used it more often for weight reduction. Despite this situation, large and randomized studies on its side effects and clinical efficacy have not yet been conducted. The Korea Food and Drug Administration conducted an experiment on the efficacy and toxicity of aloe through an animal test; however, the results showed no significant difference between animals treated with aloe vera gel and control animals.[5,6]

We searched on PubMed for a similar case related to aloe. Using the phrase 'Aloe and hepatitis,' we found five case reports and seven patients (Table 1). The first case of aloe-induced hepatitis was reported in 2005 in Germany.[7] In the

total of eight cases, including our case, the patients had taken aloe for weight reduction and as a dietary supplement.[7-11] They were diagnosed with aloe-induced toxic hepatitis because their liver biopsy results negated infection as well as auto-immune and metabolic liver diseases. There were two male and six female patients. Their average age was 46.9 years, and their average aloe consumption period was 60.4 weeks. The type of liver injury was determined through the R ratio (serum activity of ALT/ serum activity of ALP), and three types of acute liver injury by a drug or herb were found: hepatocellular, cholestatic, and mixed types.[3] All of the patients had the hepatocellular-type acute liver injury. The RUCAM scale was scored as probable in six patients, and definite in two patients. One of the eight patients had re-consumed aloe. A liver biopsy was performed in all of the eight patients, and acute hepatitis was observed. All eight patients showed improved conditions after discontinuing their intake of aloe.

Three patients in the previous domestic cases were female and over 50 years old. However, our patient was a young woman who had taken aloe for weight reduction. Our case was characterized as the hepatocellular-type because the R ratio was 15.

In the previous reports of aloe-induced toxic hepatitis, there was no case of aloe-induced toxic hepatitis related to leukopenia and thrombocytopenia. In our case, however, leukopenia and thrombocytopenia were observed upon admission. The WBC and platelet count showed a gradual increase to their normal levels after the liver function test results improved (Fig. 3B). The thrombocytopenia was thought to have been due to hypersplenism from acute hepatitis. Because of the early hematologic improvement after admission, no bone marrow evaluation was performed. Acute viral hepatitis may induce hepatitis-associated aplastic anemia[12]; however, in our case, lymphocytopenia was not observed and other causes of leukopenia, as well as thrombocytopenia were not observed besides aloe vera induced hepatitis. The lower-limit level of the reticulocyte count and the <2.0 reticulocyte production index were thought to have shown bone marrow hypoproliferation.[13] In addition, the relatively rapid restoration of WBC and platelet after the discontinuation of aloe vera may indicate transient bone marrow suppression by acute hepatitis[12] and a rare adverse effect of herbal medication, although there are few reports of such, except with quinidine-containing beverages.[14]

There are two proposed pathogeneses of drug-induced hepatitis: direct toxicity and hypersensitivity.[15] Hypersensitivity is more likely to be responsible for aloe-induced hepatitis.[16] It is supported by eosinophils in the hepatoportal area, as seen in the biopsy. However, as finding the exact real ingredients of the aloe vera products currently in circulation is very difficult, the mechanism of the relationship between aloe and liver injury cannot be easily explained. A previous report of aloe-induced liver injury suggested that the secondary reaction to contamination with *Bacillus subtilis* and chemical additives can lead to toxic hepatitis after the use of aloe vera product.[17]

People are taking more and more aloe products without keeping in mind the side effects of functional health foods, such as liver injury. Most patients do not think of functional health foods as real medicine and medical supplies, thus, they do not mention it when they are asked by physicians what medications they are taking. Therefore, physicians should always consider functional health foods as a probable cause of liver injury. In addition,no precise systematic research on aloe toxicity and efficacy has been conducted; therefore, additional studies on aloe toxicity and powerful monitoring of the side effects of aloe products are needed.

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