

CASE REPORT

A Case of Severe Drug-induced Liver Injury Caused by Over the Counter Herb (Cinnamon): Review of Literature

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ABSTRACT

A case of severe drug-induced liver injury caused by over the counter (OTC) herb medicine, is reported here. A 40-year-old male took herb drugs "Za ga-doKowa®," "Ohta-Isan®." These two drugs contained the same two herb medicines (cinnamon, fennel). About 4 months later after taking medicine, jaundice appeared. Prothrombin time activation (PT) was 45%, aspartate transaminase (AST) was 1104 IU/l, and total bilirubin (T-bil) 14.7 mg/dL. Serum tests for hepatitis viruses (A, B, C, E) were negative. Lymphocyte stimulating test was positive for Za ga-do Kowa® and Ohta-I Isan®. Liver 3D constructed by construct-CT revealed findings of the potato-like liver. The liver biopsy specimen revealed multilobular hepatic necrosis accompanied by scar formation, severe zonal degeneration and necrosis of hepatocytes mainly in the central area of the lobule.

In the reported 13 cases of cinnamon-induced liver diseases, there has been a severe abnormality of PT and T-bil. Biopsy findings of these cases showed wide ranges of necrosis. Liver injury due to cinnamon shows very severe damages, and the possibility of liver failure due to cinnamon may be imminent.

Keywords: Cinnamon, Drug-induced liver injury, Herb medicine, Over-the-counter, Severe hepatitis.

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INTRODUCTION

Herb medicines have been attaining considerable popularity in Japan because of their so-called safety and widespread availability. Several drugs of herbal origin are now available as OTC drugs. However, increasing evidence have been piled up about their adverse effects. Also, it is known that the ratios of liver injury and adverse effects are very high with the OTC herb medicine than legitimate medical herb medicine.¹

Here, we report a case of severe drug-induced liver injury (DILI) caused by OTC herb medicine (Za ga-do Kowa® and Ohta-Isan®). These drugs are available commercially at almost all places of Japan. Finally, we have accomplished a literature review with cases like the reported one.

CASE REPORT

The patient that has been reported here was a 40-year-old male. Chief complains were an epigastric pain, abdominal

bloating in postprandial time, and progressive increase of darkish color of his urine. The previous history of illness was not contributory to his present illness. Family history revealed that his uncle had colon cancer and lung cancer, however, a family history of hepatitis or jaundice or liver diseases could not be substantiated. The patient was a smoker and has been consuming about 10 cigarettes per day for the last 24 years. He was a social drinker and consuming about 350 mL of beer once a week. The patient reported no history of allergy. Also, there was no history of taking nutrient supplements. He has been working in recycling industry. There was no history of previous surgery or blood transfusion.

According to the history of present illness, the patient started taking oral Za ga-do Kowa® from January 2016 for his constipation. He began to feel heartburn from around March 2016 and then started to consume Ohta-Isan® and Gasuto-ru®. From early April 2016, he frequently felt malaise as well as epigastric pain. Around mid-April 2016, he noticed yellowish skin. From May 2016, the color

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of urine was found to be dark and brown. The stool color became somewhat whitish.

Along with time and mainly from mid-May 2016, the extents of malaise feelings became exacerbated. On May 17th, 2016, he noticed considerable nausea, noticeable loss of appetite, and increasing order of malaise. On May 19th, 2016, he was admitted to a clinic for his complaints. The local clinic referred him to our department on that day, and he was admitted to Imabari Saiseikai Hospital, Ehime, Japan.

On admission, physical examination revealed that his height was 168.7 cm and weight was 84.6 kg. He was conscious of admission. The skin and bulbar conjunctiva were icteric. However, there was no murmur at heart or lung. There were marks of insect bites on extremities. Also, acne was found on the back. Bowel sounds were normal. The abdomen was flat, soft and without any noticeable tenderness. Liver and spleen were not palpable. He had a blood pressure of 116/72 mm of Hg. Pulse rate was within normal range (88 beats per minute).

The laboratory findings on admission have been shown in Table 1 and described below: aspartate transaminase (AST); 988 IU/L, alanine aminotransferase (ALT); 847 IU/L, alkaline phosphatase (ALP); 320 IU/L, gamma-glutamyl transpeptidase (-GTP); 126 IU/L, total bilirubin

(T-bil); 11.88 mg/dl, direct bilirubin (D-bil); 7.77 mg/dl, PT-activation; 58%, lactate dehydrogenase (LDH); 386 IU/L, alpha fetoprotein (AFP); 73.9 ng/mL, carcinoembryonic antigen (CEA); 2.8 ng/mL and PIVKA2; 30mAU/mL. The patient was negative for markers of acute infections (IgM type antibodies) against cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis E virus (HEV). The titers of anti-mitochondrial antibody titer [<20 (-ve)], anti-smooth muscle antibody (<20) and anti-LKM-1 antibody were negative. Serum mac-2 binding protein glycosylation isomer (M2BPGi) was 9.21 and serum hepatocyte growth factor (HGF) was 2.31 ng/mL.

Liver elastography showed VTQ: 4.0 m/s (3 times of average). This hardness corresponds to Inuyama classification F4 or more. (VTQ Reference standard value: F0 0.67 to 1.44 m/s, F1 0.81 to 1.63 m/s, F2 0.89 to 1.85m/s, F3 1.11 to 2.29m/s, F4 1.52 to 2.94m/s Multicenter 2012)). Fibro scan showed liver stiffness of 7.5kPa (just above the upper limit of normal).

Contrast CT showed the irregular atrophy of the interior ~ anterior compartment of the liver with features of fatty liver. Obvious space occupying lesion (SOL) could not be visualized in the liver. Volume rendering image of the liver revealed potato-like regrowth (potato-liver) (Fig. 1). Measurement of liver volume showed that it was 1428 mL in May 2016, 1007 mL in July 2016 and 1259 mL in November 2016. Along with the improvement of liver function, recovery of volume and augmentation of the anterior zone were seen.

The liver biopsy specimen revealed features of liver cell necrosis (multilobular hepatic necrosis) and infiltration of inflammatory cells containing relatively higher

Table 1: Laboratory data on admission

During Admission			
WBC	6300/ μ L	NH4	90 μ g/mL
RBC	4400000/ μ L	AFP	73.9 ng/mL
Hemoglobulin	13.6 g/dL	CEA	2.8 ng/mL
PLT	209000/ μ L	CA19-9	109/8U/mL
Atypical Ly	0.5%		
ALT	847 IU/L		
AST	988 IU/L		
LDH	392 IU/L		
ALP	320 IU/L		
T-GTP	126 IU/L		
CRP	0.73 mg/L		
ESR	2-8 mm/hour		
Ferritin	472.8 /mL		
Fe	260 μ g/mL		
Ceruloplasmin	30.3 mg/dL		
CHE	216 IU/L		
TG	145 mg/dL		
HDL-C	11 mg/dL		
LDL-C	94 mg/dL		
Albumin	3 gm/dL		

WBC, White blood count; RBC, Red blood corpuscle; PLT, Platelet; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; ALP, Alkaline phosphatase; T-GTP; Glutamyl transpeptidase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; Fe, Iron; CHE, Cholinesterase; TG, Triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; NH4, ammonia; AFP, Alpha feto protein; CEA, Carcinoembryonic antigen

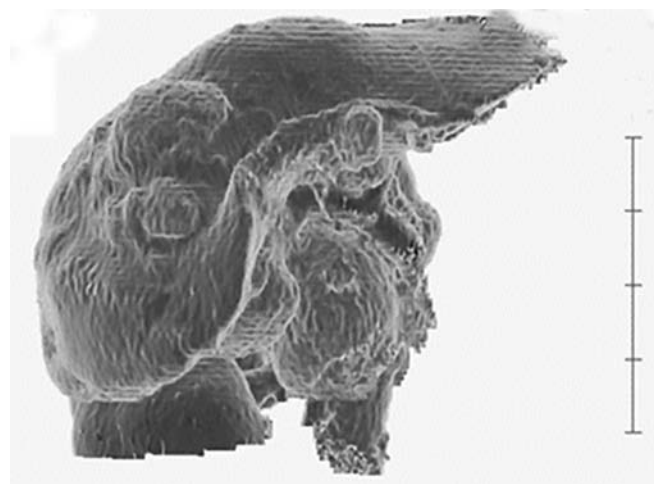
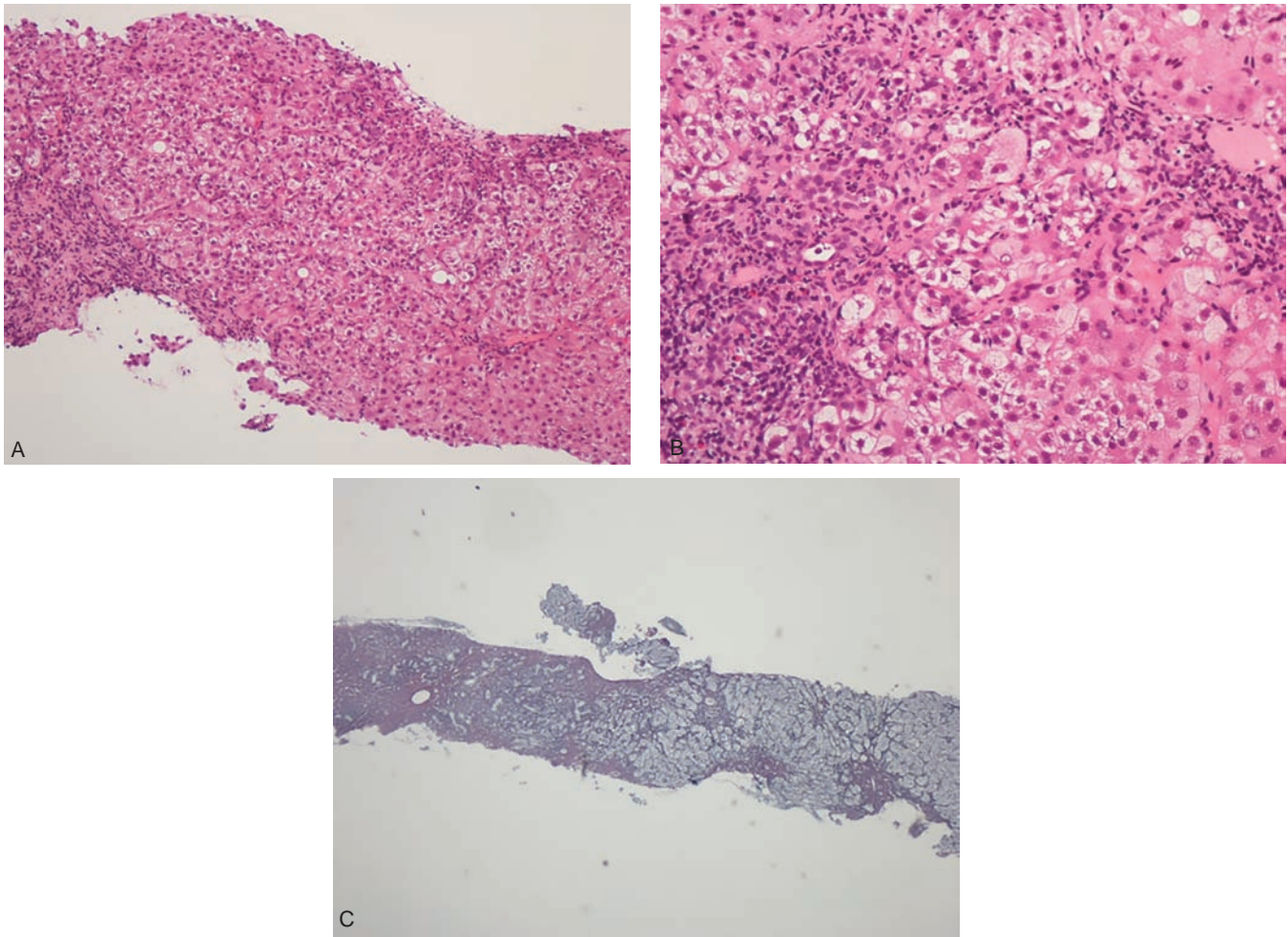


Fig. 1: Volume rendering imaging of the liver showing a potato liver. It is the liver on the 51st day after hospitalization. Volume rendering image (Liver 3D construction image by Vincent) revealed the irregular atrophy at the liver interior ~ anterior compartment and potato-like regrowth



Figs 2A to C: (A) Liver biopsy specimen showing inflammatory cell infiltration with relatively high proportions of lymphocytes (small number of eosinophils and neutrophils); (B and C) There were partially bridging necrosis and fibrosis in liver biopsy specimen.

ratios of lymphocyte accumulation (Fig. 2A). Partially bridging fibrosis, hyperplasia of cholangiole, and expansion of fibrous portal areas was also shown (Figs 2B and C). Vacuolation of the nucleus of liver cells (glycogen nucleus) were few and fatty depositions was negligible. Features of cholestasis and iron deposition could not be marked. The findings of liver biopsy were compatible with a diagnosis of DILI.

As all serum viral markers including hepatitis viruses (A, B, C, and E) were negative, we performed the drug lymphocyte stimulation test (DLST). DLST for Za ga-do Kowa® and Ohta-Isan® were positive, however, that for Gaster® was negative. Cinnamon and fennel are components common to Za ga-do Kowa® and Ohta-Isan®, and they showed borderline stimulation (Table 2). Drug-induced liver injury score (DDW-J 2004) was four points.²

After admission, the patient stopped taking medicine. Subjective symptoms gradually disappeared. However, it was the sixth week after hospitalization, the liver enzyme rises and bilirubin re-elevation started. At one time PT became 45% and T-bil increased to 14.8mg/dL.

It presented a severe liver injury. After that, we were given ursodeoxycholic acid and late evening snack (LES) therapy. We continue treating in a protective way for liver, and the patient left the hospital after 15th week when the levels ALT and AST came below 100 IU/L, and the levels of serum bilirubin decreased to 4 mg/dL.

Table 2: Drug-induced Lymphocyte Stimulation Test

Za ga-doKowa® Sceichojo PC	Drug	Ohta-Isan	
Simulation index	1.8	Simulation index	1.9
Maximum reaction level	271 CPM	Maximum reaction level	399 CPM
Free Culture	154 CPM	Free Culture	211 CPM
PHA Culture	4673	PHA Culture	98041
Cinnamon		Fennel	
Simulation index	1.4	Simulation index	1.5
Maximum reaction level	296 CPM	Maximum reaction level	322 CPM
PHA control	216 CPM	Free Culture	216 CPM
PHA Culture	172028	PHA Culture	172028 CPM

PHA, phytohemagglutinin; CPM, count per minute

Table 3: Review of literature

Drug	Age	Sex	Total bilirubin	Alanine aminotransferase	Alkaline phosphatase	Reference
Kinsigan	51	F	1.5	634		5
Kinsigan	46	F	0.8	207	129	5
Kinsigan	59	F	1.3	829		6
Kinsigan	62	M	17.7	2002	294	7
Kinsigan	27	F	28.5	166		8
Kinsigan	66	F	0.5	358	356	9
Kinsigan	54	F	38.3	822	256	10
Saireitou	57	F	8.5	1077	311	11
Shikokeisikankyoutou	47	F	4.3	1112	356	12
Shikokeisikankyoutou	42	F	2	1167	686	13
Kaigen	66	M	14.7	1104	399	14

DISCUSSION

The study presented here provides strong evidence that Za ga-do Kowa® and Ohta-Isan® might be responsible for liver injuries of this patient. First, the patient has been consuming these two drugs, and he was negative for the relevant markers of viruses that may cause acute hepatitis. The next, cessation of these drugs resulted in improvement of liver functions and the patient ultimately went back home without any specific therapy. Also, the patient showed positivity of DLST to these two herbal drugs. Taken together, this is a case of DILI possibly caused by two OTC herb drugs.

The common components of these two herb drugs are cinnamon and fennel. Ten mg of cinnamon and fennel is included in one dose of Za ga-doKowa®. On the other hand, 90 mg of cinnamon and 24 mg of fennel are included per one dose of Ohta-Isan®. In this patient, liver damage progressed by adding Ohta-Isan®. DLST showed borderline positivity to cinnamon and fennel. The possibility of the false negativity of DLST is a reality, and it is difficult to assess the real impact of DLST by one testing.²⁻⁴ However, the case history strongly indicates a role of these components in inducing DILI in this patient. There is a lack of information about fennel-induced DILI. However, there are some reports of DILI caused by cinnamon.

The liver injury caused by cinnamon has been reported previously (searched via igaku-chuo-zasshi),⁵⁻¹⁵ (Journal in Japanese). The history and details of the present patient are compatible with the reported patients in the literature (Table 3). Cinnamon usually induces severe liver injury (high level of serum total bilirubin, low levels of prothrombin time, multilobular hepatic necrosis). It has also been shown that coumarin in cinnamon has the hepatotoxicity, and a warning is given to the excessive intake with the food supplement in Germany from 2006.¹⁶

As of today, the commercial market of Chinese herbal medicine is about around 141 billion yen and this rep-

resents about 2% of market sizes of the whole medical supplies. The use of Chinese medicine is on a growing trend compared to other drugs (37% vs. 7%) in the last 6 years (2006–2012).^{17,18} Under these realities, there must be more works about the adverse effects of herbal drugs.

Also, in Relief System for Sufferers from Adverse Drug Reactions, the hepatobiliary disorder happened with Chinese medicine is placed next to a central nervous system medicine. And approximately 30% was caused by the usage of Chinese medicine available in the OTC.¹⁹ Also, liver injury represents the major side effects of OTC drugs (about 41.4%).¹

In conclusion, we presented a case of severe hepatitis due to the cinnamon from herb medicine of OTC drug. Liver injury due to cinnamon shows a very severe type of DILI. Immediate and emergency public health measures and health different health education measures should be adopted to make rationale usage of OTC-based Chinese herbal drugs.

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