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CASE REPORT

Lesser celandine (pilewort) induced acute toxic liver injury: The first case report worldwide

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Abstract

Lesser celandine, also known as *Ranunculus ficaria*, is a herbaceous perennial plant that commonly utilizes piles and is taken either internally or used externally. The causality assessment of several reports provided evidence for the existence of Greater Celandine hepatotoxicity. However, there hasn't been any case report published thus far, about lesser celandine induced liver injury. Here, we present a case of 36-year-old woman admitted to the hospital with acute hepatitis and jaundice on her sclera with no history of drug abuse or alcohol consumption. However, the patient had a recent history of lesser celandine extract consumption for hemorrhoids, for about 10 d, prior to the admission. Viral hepatitis, autoimmune hepatitis, and drug induced toxic hepatitis were ruled out by further imaging studies and laboratory analysis. Using the Council for International Organizations of Medical Sciences scale, the type of liver injury was assumed as hepatocellular and was scored as 7 which shows probable causality. Immediate discontinuation of lesser celandine extract resulted in rapid decrease of the elevated enzymes. Herbs have been reported to cause liver injury and therefore should be suspected in the case of acute hepatitis with an unknown etiology. This case is important to be the first to explain hepatotoxicity caused by lesser celandine. Physicians should consider lesser celandine as a causative agent for hepatotoxicity.

Key words: Celandine; Acute liver toxicity; Hepatitis; Pilewort; Herb

Core tip: Herbs have been reported to cause liver injury and therefore should be suspected in the case of acute hepatitis with an unknown etiology. This case is the first to explain hepatotoxicity caused by lesser celandine. Physicians should consider lesser celandine as a causative agent for hepatotoxicity.

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INTRODUCTION

Numerous herbs can be hepatotoxic. This has been demonstrated by several case reports, case series and literature reviews[1-4]. However, the potential hepatotoxicity of a variety of chemicals in any herb and case presentations lacking diagnostic exclusion made it difficult to have a clear clinical assessment[5].

Greater Celandine (*Chelidonium majus L.*) has been used in traditional Chinese medicine as weel as in the Western world for its numerous biological activities[6,7]. Teschke *et al*[8,9] reviewed several reports from Europe regarding Greater Celandine (Chelidonium majus) hepatotoxicity. The causality assessment of these reports provided evidence for the existence of Greater Celandine hepatotoxicity[8,9].

Lesser celandine, also known as *Ranunculus ficaria*, is a herbaceous perennial plant. Lesser celandine is a herbal astringent that commonly utilizes piles and is taken either internally or used externally, and for this feature it is also known as pilewort[10]. A review of literature revealed that there hasn't been any case report published thus far, about lesser celandine induced liver injury. Here, we present the first case of toxic hepatitis associated with lesser celandine consumption.

CASE REPORT

A 36-year-old woman was admitted to the hospital for acute hepatitis. Her past medical history and family history did not reveal any significant disease. She did not have any history of alcohol consumption or drug abuse. However, the patient had a recent history of lesser celandine extract consumption for hemorrhoids, for about 10 d, prior to the admission. A detailed anamnesis showed that the patient consumed lesser celandine as tea, one cup per day for 3 d. Physical examination revealed jaundice on her sclera. Laboratory abnormalities included alanine aminotransferase (ALT 1830 IU/L; normal range: 0 to 45 U/L), aspartate aminotransferase (AST 1520 IU/L; normal range: 0 to 45 U/L), alkaline phosphatase (ALP 225 IU/L; normal range: 30 to 120 U/L), and total bilirubin (3.4 mg/dL; normal range: 0.174 to 1.04 mg/dL). Anti-HBs IgG was positive, anti-HCV, HCV PCR, Anti-HAV IgM, and anti-HEV IgM were negative. There was no serologic evidence for recent infections with herpes simplex virus (HSV), epstein-barr virus (EBV), cytomegalovirus (CMV), or varisella zoster virus (VZV). Autoimmune marker analysis included anti-nuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-neutrophil cytoplasmic antibodies (ANCA), smooth muscle antibody (SMA), liver kidney microsomal antibody type 1 (LKM-1) and all markers were found to be negative. Abdominal ultrasonography was normal. Liver biopsy wasn't performed, because the patient did not give an informed consent for the procedure. Lesser celandine extract was immediately discontinued. Using the Council for International Organizations of Medical Sciences scale (CIOMS), the type of liver injury of our case was assumed as hepatocellular (ALT > 5N and R $\geqslant$ 5) and was scored as "7: probable" (Table 1)[11]. After discontinuation of lesser celandine, rapid recovery was observed in patient and liver enzyme levels returned to normal in 3 wk.

DISCUSSION

Hepatocellular, cholestatic, and mixed type (hepatocellular and cholestatic) injuries are the three types of herb induced liver injuries[12]. In the decision of different injury types, ratio R (ALT/ALP activity at the time liver injury is suspected, activity is measured by multiples of the highest point of the normal values) is used. If ALT > 2N or R $\geqslant$ 5, hepatocellular injury is assumed; if ALP > 2N or R $\leqslant$ 2, injury is cholestatic; if ALT > 2N and ALP is increased, with R > 2 and R < 5, mixed injury is assumed[11]. There are no diagnostic tests or specific criteria for herb induced hepatotoxicity. Careful history taking, insightful evaluation of laboratory findings and histopathology are essential for diagnosis. Liver biopsy might be helpful for the assessment of liver injury, however Teschke *et al*[13] reported that it is not essential for the diagnosis. The best way to determine causal agent is re-challenging. But this, for obvious reasons, is not ethically acceptable.

Lesser celandine can easily be confused with greater celandine. A case report from Germany provides an evidence for that by presenting a case with toxic hepatitis caused by greater celandine, however mentioning the name of the herb as lesser celandine in the abstract[14]. Herbs have been reported to cause liver injury and therefore should be suspected in the case of acute hepatitis with an unknown etiology. Our case suggests that physicians should consider lesser celandine as a causative agent for hepatotoxicity.

COMMENTS

Case characteristics

A 36-year-old woman was admitted to the hospital for fainting and a prior diagnosis of acute hepatitis from another hospital. She had a recent history of lesser celandine extract consumption for hemorrhoids, for about 10 d prior to the admission.

Clinical diagnosis

Physical examination revealed jaundice on her sclera.

Differential diagnosis

Viral hepatitis, autoimmune hepatitis and drug induced toxic hepatitis were

Table 1 Score of the presented patient according to Council for International Organizations of Medical Sciences Scale

Items for hepatocellular injury	Score	Result of the presented case[1]
1 Time to onset from the beginning of the drug/herb		
5-90 d (rechallenge: 1-15 d)	2	+
< 5 or > 90 d (rechallenge: > 15 d)	1	-
Alternative: Time to onset from cessation of the drug/herb		
≤ 15 d (except for slowly metabolized chemicals: > 15 d)	1	-
2 Course of ALT after cessation of the drug/herb		
Percentage difference between ALT peak and N		
Decrease ⩾ 50% within 8 d	3	+
Decrease ⩾ 50% within 30 d	2	-
No information or continued drug/herb use	0	-
Decrease ⩾ 50% after the 30th day	0	-
Decrease < 50% after the 30th day or recurrent increase	-2	-
3 Risk factors		
Alcohol use (drinks/d: > 2 for women, > 3 for men)	1	-
Alcohol use (drinks/d: ⩽ 2 for women, ⩽ 3 for men)	0	+
Age ⩾ 55 yr	1	-
Age < 55 yr	0	+
4 Concomitant drug(s) or herbs(s)		
None or no information	0	-
Concomitant drug or herb with incompatible time to onset	0	+
Concomitant drug or herb with compatible or suggestive time to onset	-1	-
Concomitant drug or herb known as hepatotoxin and with compatible or suggestive time to onset	-2	-
Concomitant drug or herb with evidence for its role in this case (positive rechallenge or validated test)	-3	-
5 Search for non drug/herb causes	"+" if negative	-
Group I (6 causes)		
Anti-HAV-IgM	+	-
HBsAg, anti-HBc-IgM, HBV-DNA	+	-
Anti-HCV, HCV-RNA	+	-
Hepatobiliary sonography/colour doppler sonography of liver vessels/endosonography/CT/MRC	+	-
Alcoholism (AST/ALT ⩾ 2)	+	-
Acute recent hypotension history (particularly if underlying heart disease)	+	-
Group II (6 causes)		
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases	+	-
Infection suggested by PCR and titer change for CMV (anti-CMV-IgM, anti-CMV-IgG)	+	-
EBV (anti-EBV-IgM, anti-EBV-IgG)	+	-
HEV (anti-HEV-IgM, anti-HEV-IgG)	+	-
HSV (anti-HSV-IgM, anti-HSV-IgG)	+	-
VZV (anti-VZV-IgM, anti-VZV-IgG)	+	-
Evaluation of group I and II		
All causes-groups I and II - reasonably ruled out	2	+
The 6 causes of group I ruled out	1	-
5 or 4 causes of group I ruled out	0	-
Less than 4 causes of group I ruled out	-2	-
Non drug or herb cause highly probable	-3	-
6 Previous information on hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	2	-
Reaction published but unlabelled	1	-
Reaction unknown	0	+
7 Response to unintentional readministration		
Doubling of ALT with the drug/herb alone, provided ALT below 5N before reexposure	3	-
Doubling of ALT with the drug(s) and herb(s) already given at the time of first reaction	1	-
Increase of ALT but less than N in the same conditions as for the first administration	-2	-
Other situations	0	+
Total Score		7

[1]The score of the patient for each 7 item for hepatocellular injury was indicated as "+" in the correspondent cell. HBV: Hepatitis B virus; HCV: Hepatitis C virus.

ruled out.

Laboratory diagnosis

Alanine aminotransferase (ALT 1830 IU/L; normal range: 0 to 45 U/L), aspartate aminotransferase (AST 1520 IU/L; normal range: 0 to 45 U/L), alkaline phosphatase (ALP 225 IU/L; normal range: 30 to 120 U/L), and total bilirubin (3.4 mg/dL; normal range: 0.174 to 1.04 mg/dL) were assessed. Anti-HBs IgG was positive, anti-HCV, HCV PCR, Anti-HAV IgM, and anti-HEV IgM were negative. There was no serologic evidence for recent infections with herpes simplex virus, epstein-barr virus, cytomegalovirus, or varisella zoster virus. All autoimmune markers were negative.

Imaging diagnosis

Abdominal ultrasonography was normal.

Treatment
Lesser celandine extract was immediately discontinued.

Related reports
This is the first case of toxic hepatitis associated with lesser celandine consumption.

Term explanation
Greater Celandine (*Chelidonium majus L.*) is a perennial herb and is used in western phytotherapy and traditional Chinese medicine for its wide variety of biological activities. Lesser celandine, *Ranunculus ficaria* (syn. *Ficaria verna, F. ranunculoides* or *F. grandiflora*), also known as pilewort, is a herbaceous perennial plant.

Experiences and lessons
Herb induced liver injury is an important problem in clinical setting, because it can be an etiology of undiagnosed acute hepatitis. This case is important to be the first to explain hepatotoxicity caused by lesser celandine. Physicians should consider lesser celandine as a causative agent for hepatotoxicity.

Peer review
Lesser celandine (pilewort) induced acute toxic liver injury by Bulent Yilmez *et al* is a relatively good and interesting report.

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