Acute hepatitis induced by greater celandine (chelidonium majus)

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To the editor,

Herbal drugs have become increasingly fashionable, are commonly used as over-the-counter remedies and are generally believed to be harmless. Nevertheless there is an accumulating body of evidence that these drugs frequently cause toxicity, as shown in the following case.

A 58-year-old woman was seen on consultation because of painless jaundice with dark urine and pale stools. She had a history of blood transfusions when delivering. Moreover she had a gastric banding for obesity in 2004 after which she lost 20 kg of weight. The last few months her weight was stable.

The jaundice started one week before consultation. There were no other complaints, there was no pruritus. She didn't drink alcohol and had smoked 5 cigarettes a day in previous years. There was no medication use beside tablets of medicinal herbs for muscular pain since 6 weeks and – started after the jaundice – supplements of vitamins. She was retired and frequently took care of her grandchildren.

On physical examination her temperature was 37°C, her heart rate was 72 beats per minute and the blood pressure was 130/80 mmHg. Her weight was 73 kg. Cardiologic auscultation was unremarkable, the lungs were clear. The jugular venous pressure was normal. The abdomen revealed a palpable and tender liver edge just beneath the costal arc. The gallbladder was also palpable.

The results of the laboratory tests are shown in Table 1. Screening for causes of hepatitis was negative (HAV, HBV, HCV, copper and caeruloplasmin, alfa-1-antitrypsin, normal serum-gamma globulin levels, negative antinuclear antibodies and negative smooth muscle-, mitochondrial- and liver/kidney microsomal antibodies).

On abdominal ultrasound the intrahepatic bile ducts seemed not dilated; there was however a suspicion of an adenopathy just above the pancreas. The gallbladder was large. A CT scan of the abdomen three days later showed an infiltrating mass from the porta hepatis to the retroperitoneum, the truncus coeliacus and the vena cava inferior. The portal veins and the hepatic artery were surrounded by this mass which also caused an obstruction of the choledochus from the porta hepatis until the head of the pancreas with secondary dilatation of the intrahepatic bile ducts. The radiologist too noticed an enlarged gallbladder.

The patient was admitted to hospital, an ERCP was performed and revealed normal bile ducts. A limited papillotomy was performed to pass the balloon catheter to be sure no choledocholithiasis was missed, given the clinical picture and the dilated bile ducts on CT scan. No stones could be evacuated. Meanwhile the jaundice had become progressive. On the forth hospital day, an explorative laparoscopy was performed to take biopsies from the liver and the mass around the porta hepatis. Macroscopic the mass were reactive adenopathies and the liver was swollen. There was minor ascites. The biopsies of the liver revealed a picture of obstructive liver disease with drop out of liver cells in zone 2 and 3, resulting in bridging necrosis (collapse). Portal tracts were large and oedematous. There was a moderate inflammatory infiltration of neutrophils and lymphocytes and an important presence of gal pigment in the residual hepatocytes. Cytologically the ascites was class two. Microscopic examination of the prelevated adenopathies confirms the diagnosis of benign reactive transformation.

On the sixth hospital day, her husband brought the medicinal herbs to the hospital : a bottle containing capsules with 50 mg of greater celandine (Chelidonium majus), 50 mg of gentian and 100 mg of curcuma root (curcumaran®, provided by Urmale). The hepatitis was ascribed to the known hepatotoxic effects of C. majus. After the admission and the withdrawal of these herbs, the liver function returned to near normal, 14 days after admission.

One week after the ERCP procedure, the patient became instable and developed melaena. Upper endoscopy revealed active bleeding in the second duodenum, which required an urgent laparatomy in order to suture a spurting vessel in the papillotomy. Four days later the laparatomy wound got infected with the presence of an abcedation requiring surgically drainage. Finally she recovered well.

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Table 1. — **Laboratory values (E. Hardeman)**

	Consultation	Admission day 1	Day 14
Hb (g/100 ml)	14.3		
White-cell count (10^9/L)	5,7		
Platelet count (10^9/L)	291		
PT %	87		
Bilirubin tot (mg/100 ml)	19,9	27.2	2.0
conj	14.0	19.4	1.2
GOT (AST) (U/L)	1740	1695	55
GPT (ALT) (U/L)	1566	1470	45
Alkaline phosph (U/L)	316	298	80
CRP (mg/100 ml)	0.8		

A CT scan after three months revealed a complete remission of the intra-abdominal adenopathies and an important decrease of the hilar mass.

Greater celandine (Chelidonium majus) is a known hepatotoxic agent, witness the fact that several cases have been described in literature (1,2,3,4). The largest series described 10 cases of acute hepatitis over a period of 2 years in Germany (1).

In some cases an unintentional re-challenge led to a second flare of hepatitis (1,2). Most cases describe a mild to severe hepatitis with frequently marked cholestasis. The duration of ingestion varies from 1 to 9 months. There is no mention of liver failure in any of the cases. Complete recovery of liver enzymes occurs about 2 to 6 months after discontinuation of the use of greater celandine.

The exact mechanism of hepatotoxicity remains unclear. An idiosyncratic reaction seems most likely since not everybody develops clinical hepatitis, there is no apparent dose dependency and the latent period is long and variable. In some cases low titers of auto-antibodies against nuclei and smooth muscle are detected, suggesting drug-induced auto-immunity (1,2). Greater celandine contains more than 20 known alkaloids, from which the exact hepatotoxic agent has not been identified yet. It is used as an antispasmodic or for its presumed choleretic effect. It is mostly prescribed for dyspepsia, irritable bowel syndrome and gallstones. There is only one single experimental study using perfused rat livers demonstrating doubled bile flow following administration of the whole ethanolic extract (5). The therapeutic effect has never been proven in controlled studies.

Remarkable in our case is the presentation with hilar adenopathies and portal oedema, mimicking an extrahepatic bile duct obstruction.

In conclusion, herbal products should always be considered as a cause of (cholestatic) hepatitis. Given the potential hepato-toxicity and the lack of evidence for a therapeutic effect, the question presents itself whether the sale of this herb should be re-evaluated.

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