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Case report

Acute hepatitis caused by a natural lipid-lowering product: When "alternative" medicine is no "alternative" at all☆

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***Background/Aims*: The general public's growing mistrust of the pharmaceutical industry and its perception of the lack of adverse effects of "natural" therapy have lead to the increasing use of "alternative drugs" for hypercholesterolemia.**

***Methods*: A sixty-three year old woman presented with severe hypertransaminasemia that had developed progressively over a few weeks. For six months she had been taking Equisterol®, an over-the-counter lipid-lowering product containing guggulsterol and red yeast rice extract. The product had been prescribed for hypercholesterolemia because the patient had developed hepatotoxicity while on lovastatin.**

***Results*: Liver biopsy revealed severe lobular necroinflammatory changes with an eosinophilic infiltrate. The episode was regarded as an adverse drug reaction after exclusion of other possible causes of acute liver disease and the prompt normalization of liver function tests after Equisterol® had been discontinued. Red yeast rice extract's cholesterol-lowering properties are largely due to fungal metabolites known as monacolins, one of which – monacolin K – is identical to lovastatin.**

***Conclusions*: The choice of an alternative medicine approach in this case subjected the patient to "re-challenge" with the official medicine agent that had previously caused mild hepatotoxicity. Physicians should keep in mind that "alternative" medicine is not always the safest alternative and sometimes it is not even "alternative."**

***Keywords*: Alternative medicine; Equisterol; Red yeast rice; Lovastatin; Hepatotoxicity; Drug-induced liver disease**

1. Introduction

Elevated serum levels of low-density lipoprotein (LDL) cholesterol are an important independent risk factor for coronary heart disease (CHD). Their reduction has been shown to lower the incidence of CHD among individuals with dyslipidemia and the frequency of CHD-related death in patients who already have CHD. The guidelines for management of hypercholesterolemia formulated by the National Cholesterol Education Program Adult Treatment Panel emphasise the use of dietary modifications, weight loss, and physical activity. Drug therapy is reserved for cases that cannot be managed with therapeutic lifestyle changes alone

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Abbreviations: CHD, coronary heart disease; LFTs, liver function tests; DILI, drug-induced liver disease.

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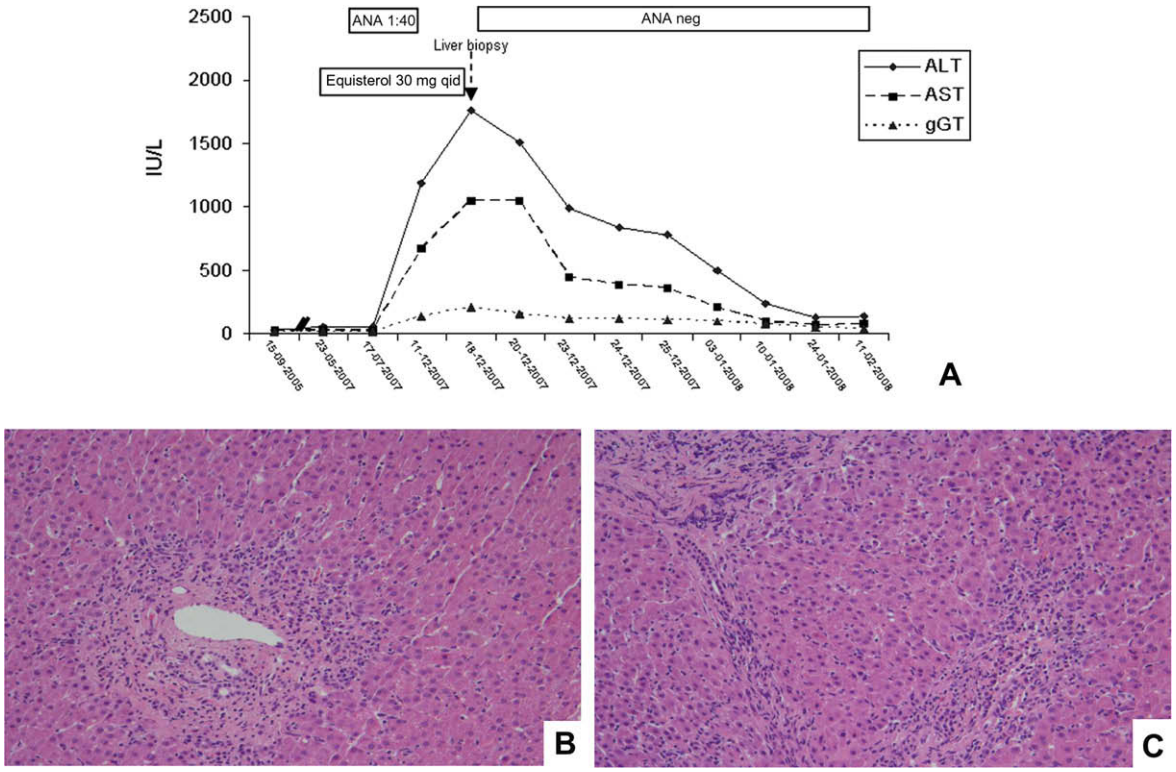

Fig. 1. (A) Clinical Chronology. Serum transaminases, γ-glutamyl transpeptidase levels and ANA titres. After discontinuation of Equisterol, liver enzymes returned to a near-normal range and ANA titres were undetectable. (B) Enlargement of the portal tracts, mild fibrosis, and bile-duct proliferation (hematoxylin and eosin, 10×). (C) Lobular disarray with liver-cell necrosis and a severe eosinophilic inflammatory infiltrate (hematoxylin and eosin, 10×).

and/or those characterised by substantial cardiovascular risk [1].

Statins are the drugs most widely used to achieve this goal. Based on the results of several meta-analyses of pooled data from randomised clinical trials and observational studies, the risk of abnormal liver function tests (LFTs) in patients on statin therapy has been estimated around 1% [2–5]. A large retrospective cohort analysis has recently shown that statin therapy is also safe for patients with pre-existing liver disease [6]. However, the public's growing mistrust of "Big Pharma" and its perception of products derived from plants as "natural" therapy with no potential for adverse effects have lead to the increasing use of "alternative drugs" for hypercholesterolemia. The truth is that use of these products can be quite dangerous, as recently illustrated by the cases of acute liver failure associated with certain dietary supplements and "naturopathic hepatoprotectors" [7–9].

We report the case of a patient who had discontinued statin therapy after developing drug-induced liver disease with hypertransaminasemia. She later developed acute hepatotoxicity as a result of treatment with a natural lipid-lowering product, which turned out to contain the same statin that had caused her prior liver disease.

2. Case report

In January 2005, a 63-year-old woman with a two-year history of hypercholesterolemia and family history of ischemic heart disease was started on lovastatin (20 mg/day). Six months later (June 2005), she was found to have mildly elevated serum transaminase levels (1.5 times higher than the upper normal limits) with a transient rise in ANA antibody titers (1:40). Investigation of the LFT alterations revealed no serological evidence of viral infection (hepatitis A, B, or E; Epstein Barr; Herpes; or Cytomegalovirus), cryoglobulins, or other auto-antibodies (AMA, LKM, EMA). The renal and thyroid profiles were normal, and there was no hepatomegaly on the abdominal sonogram. She refused to have a liver biopsy.

Lovastatin therapy was interrupted, and three months later all LFT parameters had returned to normal. For this reason, the statin was definitively discontinued, and polyunsaturated fatty acid supplementation (1 g/day b.i.d.) was started. In June 2007, her total cholesterol remained high (240 mg/dlL), and a metabolic consultant prescribed complementary therapy with a natural product, Equisterol® (Istituto Farmacoterapico Italiano S.p.A., Rome, Italy), one 30-mg tablet once a day. According to the manufacturer, Equisterol contains

guggulsterol (from the Ayurvedic medicinal plant *Commiphora mukul*); sistosterol; chlorogenic acid; policosanol (a natural substance derived from sugar cane); vitamins C, E, and B6; niacin; coenzyme Q; and 1–17 g of red yeast rice (roughly equivalent to 15 mg of monacolin).

In December 2007 she was admitted to our department for markedly elevated transaminase levels and fatigue. Her BMI was normal (24.8 Kg/m^2), and she denied all use of alcohol (a claim confirmed by her relatives). The admission laboratory work-up disclosed severe liver-cell necrosis (ALT 1760 U/L, AST 1046 U/L, normal values 7–45) with cholestasis (ALP 722 U/L, normal values 99–279; GGT 157 U/L, normal values 5–36) and hyperbilirubinemia (total 1.9 mg/dl, direct 0.9 mg/dl) (Fig. 1A). Fasting glucose, insulin, ferritin, and total cholesterol levels were within normal limits.

We excluded hepatotropic viral infections and other common causes of hypertransaminasemia. The patient was also screened for Wilson's disease and alpha-1-antitrypsin disease. ANA, AMA, anti-LKM, ASMA, serum antiendomysial antibodies, pANCA, and cANCA antibody titers were negative, but IgG levels were mildly elevated (1600–1630 mg/dL). The HLA haplotype was negative for DR3 and/or DR4. Abdominal ultrasonography showed an enlarged liver (bipolar diameter of the right lobe: 15.7 cm) with mild steatosis. The gall bladder and biliary tree were normal with no sign of lithiasis. A liver biopsy revealed severe lobular necroinflammatory changes, the presence of eosinophil granulocytes, and widening of the portal spaces with mild fibrosis. The bile ductules were characterised by proliferation and metaplasia (Fig. 1 B and C).

Equisterol was discontinued, and the patient was treated for one week with glutathione i.v. (600 mg/day) and ursodeoxycholic acid p.o. (300 mg/day t.i.d). After ten days we observed a clear reduction of both transaminases and cholestasis indices. The Doppler ultrasound scan of the carotid arteries showed no evidence of atherosclerosis. Therefore, she was discharged with instructions for appropriate lifestyle modifications, and all drug therapy was deferred because of the low cardiovascular risk.

Serum transaminase levels and cholestasis indices were monitored monthly. Six months after discharge, the former were only mildly elevated (ALT 144 U/L, AST 81 U/L), and gamma-GT and alkaline phosphatase levels were within normal limits.

3. Discussion

We report a case of unequivocal hepatotoxicity caused by a "natural" over-the-counter remedy for hypercholesterolemia in a woman who had already experienced LFT alterations during statin therapy for the same condition. The product of concern contains sterols from the Ayurvedic medicinal plant, *C. mukul* (also known as *guggul* or *myrrh*), and extract of red yeast rice. *Commiphora mukul* contains guggulsterone band E, mainly in the sterol fraction, which possesses documented cholesterol-lowering properties related to its antagonism of the farnesoid X receptor, a nuclear hormone receptor that is activated by bile acids [10]. A single case of rhabdomyolysis has been reported in a patient taking *C. mukul* extract for high cholesterol [11], but to date there have been no unequivocal cases of liver toxicity associated with the use of guggul. Therefore, we do not believe that this plant sterol is responsible for the problems experienced by our patient.

The second lipid-lowering ingredient of Equisterol is an extract of red yeast rice (cook rice fermented by the yeast *Monascus purpureus*). Its ability to reduce total cholesterol levels has been well documented [12], and its safety has been confirmed in a randomised, double-blind trial [13]. A single case of severe rhabdomyolysis has been tentatively attributed to the use of red yeast rice by a renal transplant recipient. However, this patient was also on chronic therapy with cyclosporine, and the authors of the report noted that the latter drug may have interfered with metabolism of the yeast-related sterols by cytochrome P-450 isoenzyme 3A4 [14]. Red yeast rice contains cholesterol-synthesis-inhibiting fungal metabolites known as monacolins [13]. Roughly 75% of the antihyperlipidemic activity of red yeast rice seems to be attributable to the lactone and hydroxy-acid forms of monacolin K, a metabolite of *Monascus ruber* that inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [13,15]. In 1979, monacolin K and lovastatin (then known as mevinolin) were recognized to be identical compounds produced, respectively, by *M. ruber* and *Aspergillus terreus* [16]. Five milligrams of monacolin K has been shown to be the equivalent of 20–40 mg of lovastatin [13].

In the case described here, the patient took a daily dose of monacolin K somewhere between 15 and 30 mg for at least 6 months. This is the equivalent of 60–120 mg of lovastatin, a daily dose 3–4 times higher than the one she had been taking in 2005 (20 mg/day). At that dose, the patient experienced mildly elevated transaminase levels, which spontaneously returned to normal when the lovastatin was discontinued. Therefore, the episode that led to her hospitalization in December 2007 can be regarded as a positive response to re-challenge, which is currently considered the single most accurate means for demonstrating direct causal links between drug use and liver toxicity [17]. Another case of hepatitis has recently been attributed to red yeast rice, and the laboratory and histological findings were very similar to those of our patient. This adds support

to our hypothesis that this dietary supplement produces liver damage via mechanisms similar to those underlying the hepatotoxicity of any HMG-CoA inhibitor [18].

Today, the safety of lovastatin is widely recognized. Hepatotoxic side effects are very infrequent, even in individuals with elevated liver enzymes before treatment [19]. However, premarketing and postmarketing studies have both shown that the frequency of these side effects is dose-related and almost always reversible [19–21]. It is therefore conceivable that the hepatotoxic effects we observed were similar to those that would be produced by long-term, high-dose lovastatin use (>80 mg/day). In the only reported case of this type in which a liver biopsy was obtained, the histologic findings were almost identical to those described in the present report [21].

Although cases of statin-induced autoimmune hepatitis have been reported [22–24], we do not feel that autoimmunity played any role in the present case – as an initial trigger or "booster." This conclusion is supported by the absence of autoantibodies, the spontaneous resolution of all symptoms without any specific therapy, and by the patient's HLA profile, which is not compatible with a diagnosis of autoimmune hepatitis. In fact, the possibility of autoimmune hepatitis was excluded in light of the rapid response to withdrawal of lovastatin, the patient's HLA haplotype, and the low International Autoimmune Hepatitis Group score [25].

Ayurvedic products may also be contaminated by toxic substances, such as heavy metals and arsenic, as recently reported [26]. It is impossible to determine whether the supplement used by our patient contained similar substances. As in the United States, dietary supplements are not subjected to the same rigorous controls used for pharmaceuticals. Heavy metal toxicity in particular seems to target mainly renal [27] and cognitive functions [28], and we have found no reports of hepatotoxicity caused by these contaminants.

This case highlights one major problem related to the complementary and alternative medicine market. The products sold in this market are advertised as – and considered by most patients to be – "natural substances" or "nutritional supplements" that are consequently safer than conventional drugs. However, these products often contain multiple active ingredients in poorly specified amounts, their labelling is often incomplete, and their chemical composition is only partially known by patients and physicians alike.

The toxic hepatitis described in this report was caused by the attempt to control the patient's hypercholesterolemia without resorting to conventional statin therapy, which had previously caused mild signs of hepatotoxicity. As a result, the patient was unwittingly treated with an agent identical to the statin that needed to be avoided. As this report illustrates, "alternative" medicine is not always the best alternative: sometimes, it is no alternative at all.

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