Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts following tibolone and Hypericum perforatum (St. John's wort). Case of drug interaction ?

F. Etogo-Asse, F. Boemer, C. Sempoux, A. Geubel

Departments of Gastroenterology and Pathology, Cliniques Universitaires St-Luc, Université Catholique de Louvain (UCL), Brussels, Belgium.

Abstract

The case of a patient under tibolone therapy for two years who developed a mixed-type liver injury with prolonged cholestasis and features of the vanishing bile duct syndrome following a ten weeks treatment with St. John wort (*Hypericum Perforatum*) infusions is reported. In the absence of evidence of a potential role for concomitant medication i.e. hydroxychloroquine sulfate to play a role in the clinical, biochemical and morphological picture, an interaction between the herbal preparation and tibolone was suspected as the likely cause of liver damage. (Acta gastroenterol. belg., **2008**, 71, **36-38**).

Key words : St. John's wort, *hypericum perforatum*, cholestasis, vanishing bile duct syndrome.

Introduction

St. John's wort (*Hypericum Perforatum*) is a herbal medicinal product whose use is gaining in popularity, especially for treating depression. Hyperforin and hypericin are thought to be the main active constituents. St. John's wort-induced liver toxicity has not been reported but its components are well known inducers of enzymes of the cytochrome P450 system. Enzyme induction can be responsible for a decrease of the plasma levels of a number of prescribed medications or alternatively, promote liver toxicity related to metabolites of various drugs or herbal remedies (1-8).

We report the case of a patient under tibolone therapy in whom a ten weeks course of *hypericum perforatum* infusions was followed by the occurrence of a picture of mild acute hepatitis with prolonged cholestasis and morphological evidence of the vanishing bile duct syndrome.

Case report

A 57 year old woman was referred to our Unit on Oct. 10th, 2002 for liver biopsy because of jaundice of five weeks duration. Her previous medical history was unremarkable except for clinical and serological picture of rheumatoid arthritis which appeared in 1995 and which has been treated by Hydroxychloroquine sulfate (200 mg per day) for the last 7 years. She had also been treated for the last two years with Tibolone (2.5 mg per day) as therapy of postmenopausal symptoms. In early July 2002, she initiated a treatment with *Hypericum Perforatum*, due to the occurrence of mild depression. She took an infusion of 2 g of the herbal preparation every day from July 2002 until the occurrence of fatigue, reduced appetite, dark urines, jaundice and pruritus which occurred on september 9th after the intake of infusions from 140 g of St. John's wort. Clinical features prompted a consultation in another center where the clinical examination showed jaundice, liver enlargement and skin scratching lesions. Patient's weight was 40 Kg. Biochemical work-up showed : GOT(AST) : 178 IU/L (N : 1-21), GPT (ALT) : 424 IU/L (N : 1-22), Alk. Phos. : 162 IU/L (N : 35-104), gamma-GT : 48 IU/L (N : 5-25), total s. bilirubin : 6. 3 mg/dL (N : 2-10), direct bilirubin : 3.2 mg/dL (N : < 3), gammaglobulins : 2.2 g/dL (N : 0.9-1.5), IgG : 2122 mg/dL (N : 800-1800). INR (International Normalised Ratio) was in the normal range. Serological examination for HAV, HCV, HBV, EBV, CMV and Toxoplasma was negative as well as the search for anti-smooth muscle, anti-LKM1 and antimitochondrial antibodies. Antinuclear antibodies were positive (1/320). Upper abdominal ultrasound examination was unremarkable as was an abdominal tomodensitometry. Both Tibolone and Hypericum intake were discontinued. Due to the persistence and worsening of clinical and biochemical features of cholestasis with severe pruritus and biochemical worsening she was referred to our unit for hepatic vein catheterisation and liver biopsy. Hepatic venous pressure gradient was only slightly elevated at 7 mmHg. Liver specimen examination showed portal tracts devoid of bile duct structures in 3 out of 5 together with severe centrilobular cholestasis and in the lobules, a few scattered aciphilic bodies. Immunohistochemistry for cytokeratin 7 showed a strong expression in periportal hepatocytes (Fig. 1).

The patient was treated with ursodesoxycholic acid (250 mg two times per day). Both clinical and biochemical features slowly improved, liver biochemistry normalising after slightly more than one year of follow-up (Fig. 2).

Correspondence to : A.P. Geubel, M.D., Cliniques Universitaires St-Luc, 10, Avenue Hippocrate, B-1200 Brussels, Belgium. E-mail : geubel@gaen.ucl.ac.be

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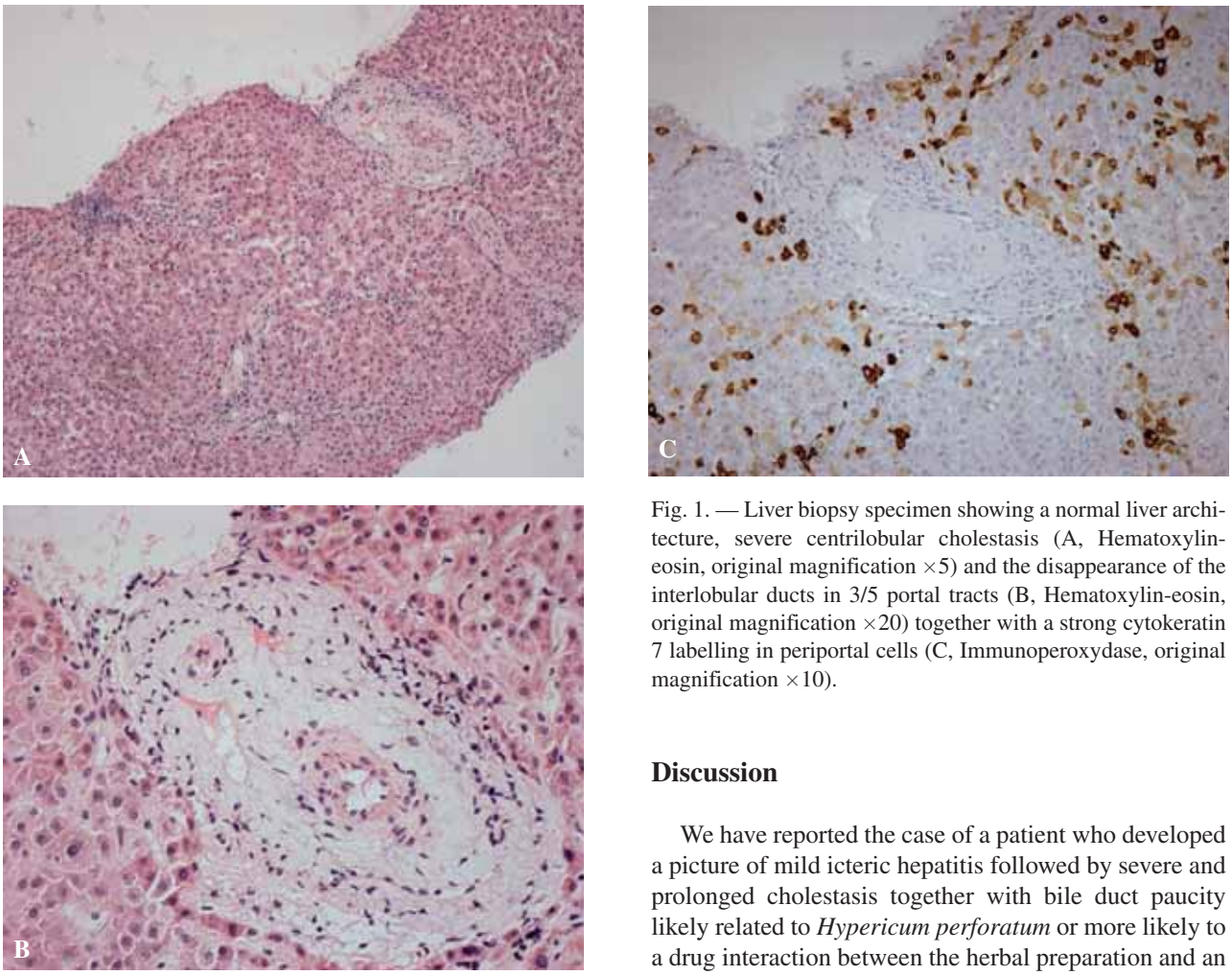

Fig. 1. — Liver biopsy specimen showing a normal liver architecture, severe centrilobular cholestasis (A, Hematoxylin-eosin, original magnification ×5) and the disappearance of the interlobular ducts in 3/5 portal tracts (B, Hematoxylin-eosin, original magnification ×20) together with a strong cytokeratin 7 labelling in periportal cells (C, Immunoperoxydase, original magnification ×10).

Discussion

We have reported the case of a patient who developed a picture of mild icteric hepatitis followed by severe and prolonged cholestasis together with bile duct paucity likely related to *Hypericum perforatum* or more likely to a drug interaction between the herbal preparation and an

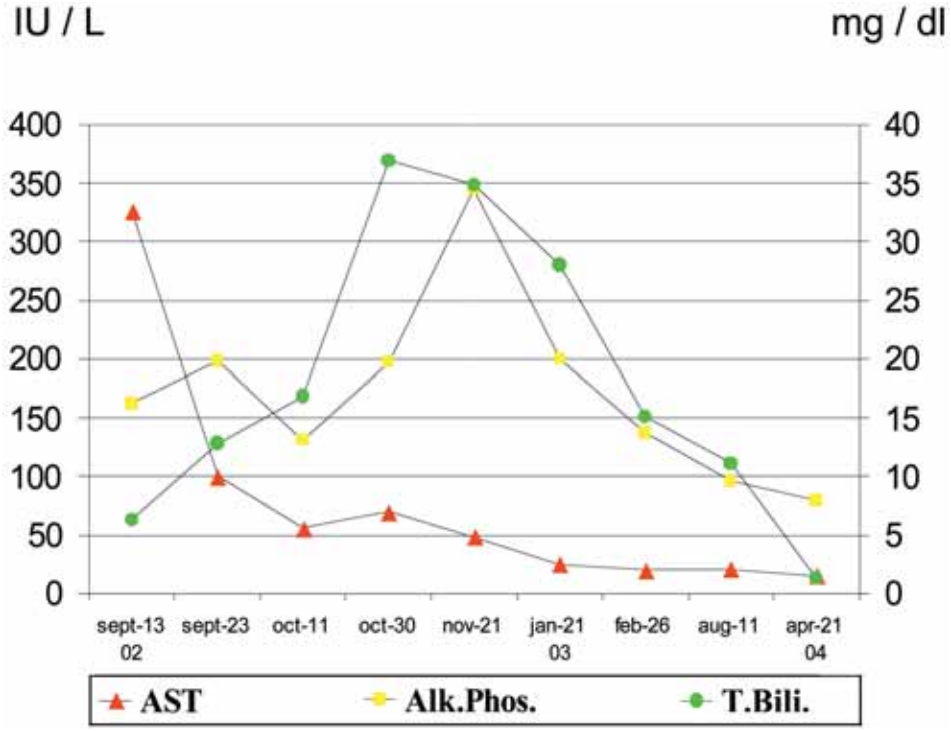

Fig. 2. — Graph showing the evolution of AST (closed triangles), Alk. Phos. (open squares) and total serum bilirubin (grey circles) from presentation (Sept. 13th, 2002) to resolution (Apr. 21th, 2004).

other concomitant medication. Jaundice appeared after ten weeks of treatment with daily infusions of 2 g of *hypericum* preparation. The disease ran a prolonged and disabling cholestatic course and the patient eventually recovered after 48 weeks. Liver histology of a transjugular liver biopsy specimen showed centrilobular cholestasis and the disappearance of interlobular bile ducts in the majority of portal spaces. Signs of chronic cholestasis under the form of hepatocellular damage believed to be related to bile salt accumulation, the so called "cholate satis" (9) were also prominent. In addition, the disappearance of interlobular bile ducts was ascertained both by a complete absence of cytokeratin 7 expression in the portal spaces and a strong cytokeratin 7 expression in cells of the periportal areas recently referred as "intermediate hepatobiliary cells" (10). Therapy with ursodeoxycholic acid was prescribed aiming at reducing cholangiolitis and "secondary" bile acids hepatotoxicity. A relatively low dose of the medication was chosen (10 mg/Kg) to avoid a potential worsening of cholestasis which might occur in such a setting.

On the one hand, St. John's wort is not known as a hepatotoxic. However, an animal study performed in rats during pregnancy or lactation showed that doses of extract close to those given for depression in human may induce severe liver and kidney damage in newborn animals exposed through pregnancy and lactation. Similar lesions were also observed in newborn animals exposed to the extract or its metabolites only through breast feeding clearly suggesting a potential for hepatotoxicity of the drug (11). In addition, a case of maternal thrombocytopenia and neonatal jaundice has been described in one case when St. John's wort was consumed during pregnancy (12). On the other hand, the herbal preparation is a well known inducer of the CYP 3A4, an effect responsible for an increase of the metabolism of various compounds including combined oral contraceptives, cyclosporin and indanavir. The mechanism of CYP 3A4 induction has been clearly related to the activation of the pregnane X receptor by hyperforin wich acts as a potent ligand of the nuclear receptor (13).

Even if a metabolic interaction with hydroxychloroquine might occur due to St. John's wort's influence on CYP3A4 (1,14) this compound is an extremely safe medication never been convincingly implicated in hepatotoxicity. On the contrary, Tibolone has been suggested as the potential cause of a single case of severe cholestatic hepatitis (15). In our patient who has been exposed to Tibolone for two years without any side-effect, the occurrence of a similar picture shortly after the introduction of St. John's wort infusions strongly suggest the existence of an interaction between the two drugs, the mechanism of which remaining to be elucidated since Tibolone is known as an only weak inhibitor of CYP3A4 (16).

In conclusion, the occurrence of a severe liver damage with the vanishing bile duct syndrome shortly after the introduction of St. John's wort infusions in a patient under Tibolone therapy strongly suggests the potential for an interaction between the two compounds. Clinicians and gynaecologists should be aware of the possible risk of prescribing both compounds especially at a time where the prescription of the herbal compound is increasing in popularity.

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