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Case Report

Case report: primary biliary cirrhosis following leptospirosis - coincidence or consequence?

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Abstract. We present the case of a 59 years old female diagnosed with leptospirosis whose clinical condition deteriorated after a short period of improvement. The clinical and explorational data were suggestive for primary biliary cirrhosis and the therapy was conducted accordingly. The particularity of our case is the diagnosis of primary biliary cirrhosis in a patient with leptospirosis who has never presented health problems related to the liver so far.

Key Words: leptospirosis, liver, primary biliary cirrhosis, autoimmune liver diseases.

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Introduction

PBC is an autoimmune liver disease resulting from the immune attack against cholangiocytes and affecting middle aged women who present fatigue, jaundice, pruritus and cholestasis (Poupon 2010). The exact cause is not well defined, but it is suspected that genetic and environment factors trigger the immune overreaction to self-structures. The hallmark of this severe condition, of poor prognosis in the lack of treatment are the AMA. Therapeutic approach includes UDCA, along with corticoids and immunosuppressants in selected cases (Poupon 2010; Lindor et al 2009). Leptospirosis is an infection caused by bacteria belonging to the genus *Leptospira*, affecting humans and different animal hosts, that involves mainly liver and kidneys but can virtually affect any organ, including endothelium and generates a polymorphic clinical condition. Diagnosis is achieved by the detection of IgM antibodies against *Leptospira*. Antibiotic therapy is usually safe and effective (amoxicillin, ampicillin, penicillin, ceftriaxone, cefotaxime ao) (Izurieta et al 2008). We present a case of PBC presumed to be triggered by a recent episode of leptospirosis. The purpose of the present paper is that of illustrating the presence of two concomitant clinical conditions as well as the possible correlations and interrelations between them.

Case presentation

A 59 years old female is admitted in Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, accusing asthenia, fatigability, yellow coloration of skin and sclera, symptoms installed within a week. A written consent was obtained from the patient for publication of the case report. Patient has been previously admitted in a territorial hospital near her location, where angiocholitis was suspected and the case was directed to our clinic. At the same time in the territorial service, viral markers (ATC-VHA, ATC-HVC, Ag HBs) with negative result and antibodies against *Leptospira* (agglutination reaction) with positive result were harvested. From medical record of the patient we retain a plurialergical status without any elements of liver pathology so far.

At the admission, the patient presented jaundice, squamous lesions on anterolateral sides of calves, grade II systolic murmur in mitral zone irradiating to axilla, mild epigastric sensibility, liver margin at 2 cm below right costal border. Biology showed hepatocitolisis (ASAT=237 U/l, ALAT=496 U/l) and cholestasis with pigment retention (AP=362 U/l, GGT=132 U/l, tBLR=4.39 mg/l, dBLR=3.67 mg/dl), mixed dyslipidemia (TSC=226 mg/dl, TG=210 mg/dl) accelerated ESR (40/80), leukocytosis (L=15.300/cm3), positive agglutination reaction for *Leptospira*, 1/256 titre of total IgG and IgM antibodies against *Leptospira* evaluated by complement fixation test, leukocyturia (25/ml), uBLR=1 mg/dl, uUBG=8 mg/dl). Liver ultrasonography revealed size within superior normal limits (RL=133 mm, LL=73 mm) with normal echogenicity and slight immunogenicity, without focal lesions or dilated biliary ducts and no abnormal changes of other organs. Prick test showed tolerance to ampicillin.

We established the diagnosis of leptospirosis, hypercholesterolemia, hypertriglyceridemia, infection of the inferior urinary tract. Therapy with ampicillin iv 4 g/day, for 14 days, combined with hepatoprotectors (aspartic acid - Aspatofort^{R} 2 vial per day iv, silibinum - Lagosa^{R} 2x1/day, orally) was administrated with favorable evolution (ASAT=182-150-120-72 U/l, ALAT=442-322-162-92 U/l, AP=348 U/l, GGT=92-56 U/l, tBLR=2.4 mg/dl).

Patient presents after a month for control accusing relapsing yellow coloration of skin and sclera. Physical exam was similar to previous admission. Biology revealed marked hepatocitolisis (ASAT=618-487-358 U/l, ALAT=473-443-411 U/l), cholestasis with pigmentary retention (tBLR=13.5-12.8-10.9 mg/dl, dBLR=9.6-8.3-7.5 mg/dl, AP=418-340-383 U/l, GGT=150-89-69 U/l), hypertriglyceridemia (TG=272 mg/dl), mild hypoalbuminemia (Alb=3.2 g/dl) with elevated alpha 1 (0.3 mg/dl) and gamma (2.2 mg/dl) globulin fractions. We also noticed high ESR (92/52) and leukocytosis (17600-8910/ml).

After testing sensibility to the drug, we initiated therapy with ceftriaxone - Cefort^{R} 1g/8h, along with hepatoprotector therapy from previous admission with slight improvement of clinical and biochemical condition. Considering the deteriorated liver tests, we suspected an autoimmune cholestatic liver condition and suggested liver biopsy but the patient refused it. In addition, we determined AMA, ANA, LKM, SMA from which AMA were positive in 1/80 titre.

Thus, we established the diagnosis of PBC and patient started therapy with Prednisone 30 mg/day and UDCA - UrsofalkR 4x250 mg/day together with omeprazole - Omeran^{R} 2x20 mg/day and low salt regimen. Although ultrasonography did not show any signs of portal hypertension the patient underwent upper digestive endoscopy which revealed no other changes except some antral erosions without the presence of Helicobacter pylori. Under the mentioned above therapy the evolution is favorable with good response of hepatocitolisis (ASAT=225-125-80 U/l, ALAT=246-120-65 U/l) and cholestasis (AP=337 U/l, GGT=65 U/l, tBLR=5.8-5.1 mg/dl, dBLR=5.4-3.2 mg/dl) and improvement of jaundice.

After six months of therapy the patient is again admitted for control, without any complains having biochemical exams within normal limits (ASAT=31 U/l, ALAT=30 U/l, tBLR=0.52 mg/dl, AP=260UI/l, GGT=49 U/l, TSC=198 mg/dl, STG=110 mg/dl, ESR=10/20). In these conditions, we choose to gradually lower corticoid doses with 5 mg per week and when the daily dose reached 5 mg we continued the treatment another month and then we stopped the administration, thus retaining the administration of UDCA. At the reevaluation exams carried along the period of time during which corticoid doses was lowered, as well as after stopping the administration and six months after stopping the administration, the patient remained asymptomatic having biochemical profile within normal values.

Discussion

We presented the case of PBC onset after an episode of leptospirosis in a 59 years old female who has never accused liver related issues until now. In fact, we may consider two possibilities: first, the leptospirosis could have triggered the autoimmune liver disease or the autoimmune disease existed in a subclinical form and bursted due to liver aggression provoked by the infection. Leptospirosis is known to mimic various clinical entities, even neoplastic diseases (Granito et al 2004), but there are cases, albeit rare, when leptospirosis is considered capable of inducing autoimmune hepatitis for instance (Urganci et al 2011). *Novosphingobium aromaticivorans* is credited with capability of inducing PBC due to a high degree of homology with human autoepitope PDC-E2, the target for AMA (Mattner at al 2008). We found in literature no further evidence of *Leptospira* being related with PBC, although there are many cases of fulminant hepatitis in patients with a subsequent liver diseases who get infected with *Leptospira* (Vetter et al 2010; Andreadis et al 2010). On the other hand, leptospirosis could be the cause of certain cases of cryptogenetic hepatitis (Rizvi et al 2011). We also found in this patient elevated values of serum cholesterol and triglycerides so the befitting approach would have been the introduction of statins but we avoided this option due to the liver disease having in mind the hepatotoxicity of these drugs (Younoszai et al 2014). Contradictorily, recent studies confirmed some benefits of statins in persons with liver disease and do not advise limitations of statins use in person with compensated liver diseases (Abu Rajab et al 2010). Anyway, the lipid profile improved after a short period of time so this issue did not consist a matter of consideration. The gold standard of diagnosis in similar cases is hepatic biopsy which elucidates the diagnosis and reveal the magnitude of biliary injury (Poupon et al 2010) but the patient refused the procedure. With positive AMA, we established the diagnosis but we would have serious difficulties in a seronegative form of PBC. Having in mind that the patient's clinical and biological status improved after antibiotic therapy and then worsened with more severe biochemical changes, we may conclude that leptospirosis triggered the onset of PBC, considering the cases of liver disease after immune or autoimmune phenomena mentioned above. In our opinion leptospirosis could have induced some immunologic changes and could have elapsed the autoimmune process. We encountered a similar case report whose author suspected *Coxiella burnetii* as a possible trigger for AH-PBC overlap syndrome (Kaech et al 2009). As a conclusion, we must stress upon the fact that leptospirosis is an important health problem, at least in some regions (Pages et al 2014), and could mimic a lot of hepatic and non-hepatic conditions so it is a diagnosis possibility that at least in selected cases must be taken into account. In this case, sophisticated methods of molecular biology and genetics (*Leptospira* DNA, liver electron microscopy, immunity markers ao) (Chaudhry et al 2013; Eshghi et al 2012) could have provided interesting data for scientific research purpose. The novelty of our paper lies in the reporting of autoimmune hepatitis following a leptospirosis episode after a short period of improvement in a patient who has never had any liver diseases before.

Conclusions

In cases of proper treated liver disease if the patient status does not improve or it worsens we should suspect a subsequent disease or an overlapped one.

Abbreviations

PBC = primary biliary cirrhosis, AH = autoimmune hepatitis, AMA = antimitochondrial antibodies, UDCA = ursodeoxicholic acid, Ig M/G = immune globulins class M/G, PDC-E2 = Pyruvate Dehydrogenase Complex E2, Atb = antibodies, HAV = hepatitis A virus, HCV = hepatitis C virus, AgHBs = HBs antigen, ASAT = aspartataminotransferase, ALAT = alaninaminotransferase, AP = alkaline phosphatase, GGT = gamma-glutamyl transpeptidase, t/d BLR = total/direct serum bilirubin, uBLR = urinary bilirubin, uUBG = urobilinogen, TSC = total serum cholesterol, STG = serum triglycerides, ESR = erythrocyte sedimentation rate, R/L

L= liver right/left lobe, ANA = antinuclear antibodies, LKM = anti liver kidney microsomal antibodies, L = leukocytes, SMA = anti-smooth muscle antibodies, DNA = deoxyribonucleic acid.

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