Cholestatic hepatitis after diagnostic ajmaline challenge

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Abstract

We report a cholestatic hepatitis in an elderly woman after ajmaline challenge during electrophysiological testing for Brugada syndrome. No other medication was reported in the previous 6 months of the onset of jaundice. Liver biopsy showed a cholestatic hepatitis with mild biliary damage. Liver enzymes normalized within 2 weeks as well as jaundice. To the best of our knowledge this is the second case of histologically proved cholestatic hepatitis induced by intravenous ajmaline testing. (Acta gastroenterol. belg., **2017**, 80, **425-426**).

Key words : Ajmaline, cholestatic hepatitis.

Case presentation

A 78 year old woman was referred to our clinic with painless jaundice. Detailed treatment inquiry revealed occasional paracetamol use (2 grams a day maximum) for arthralgia. Her regular treatment included levothyroxin, ramipril, simvastatine, rivaroxaban and clotiazepam since at least 6 months without any recent modification, and no antibiotic therapy was recently reported. Medical history was marked by arterial hypertension, hypercholesterolemia, mitral insufficiency and atrial fibrillation. She denied drinking alcohol, and there was no use of recreational drugs or herbal therapies.

One month before the onset of symptoms, the patient was admitted in the cardiology unit for syncope investigation. She underwent diagnostic ajmaline challenge as screening for Brugada syndrom and received 1 mg/kg of ajmaline during electrophysiology testing. No additional drug was administered or added to her existing treatment.

Clinical examination revealed jaundice without hepatomegaly nor stigmata of chronic liver disease. Blood pressure and other vital parameters were normal. Biochemistry showed elevated liver enzymes with 2 fold higher transaminases, and cholestasis was 3-4 fold higher than normal. Bilirubin peaked at 140.2 mmol/l at day 42 after Ajmaline injection (Fig. 1). Complete blood count, prothrombin time, kidney function, inflammatory markers, and ionogram remained within normal limits throughout. Plasma albumin was unchanged compared to 8 months before symptoms while liver enzymes were normal. Serology tests for viral hepatitis (A, B, C, E, CMV, EBV) and auto-immune markers (anti-mitcochondrial antibody, anti-smooth muscle antibody, and antinuclear antibody) were negative.

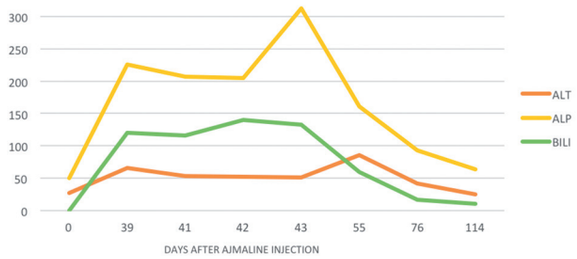

Fig. 1. — Level of liver enzyme (1U/ml) and bilirubin (mmc./l) after Ajmaline administration. ALT : Alanine aminotransferase. ALP : Alkaline phosphatase. BL1 : Bilirubin.

Abdominal ultrasound demonstrated normal appearance of liver parenchyma, no distension of intrahepatic or extrahepatic bile ducts, and there was no portal thrombosis. Abdominal tomography was also unremarkable. Liver, pancreas and bile ducts appeared normal.

Echoendoscopy ultrasound of the upper digestive tract was normal. Main bile duct measured 6 mm, and no gallstones were visualised.

A liver biopsy was finally performed and showed intra-canalicular bilirubinostasis with mild biliary damage and cholate stasis (Fig. 2), which is consistent with a cholestatic drug-induced liver damage.

Results of liver biopsy led us to a through investigation of her recent treatments. Ajmaline was the only new drug documented over the last 6 months. Jaundice decreased 2 weeks after symptoms onset, and bilirubin and liver enzymes normalized into 10 weeks.

Backround and discussion

Ajmaline is an alkaloid found in the root of Rauwolfia serpentina, among other plant sources.1 It was first described in 1931 and had been used as an antiarrythmic agent for about 50 years in the management of atrial fibrillation in patients with Wolff-Parkinson-White syndrome and also for treatment of ventricular tachycardia. Ajmaline is a class Ia antiarrhythmic agent according

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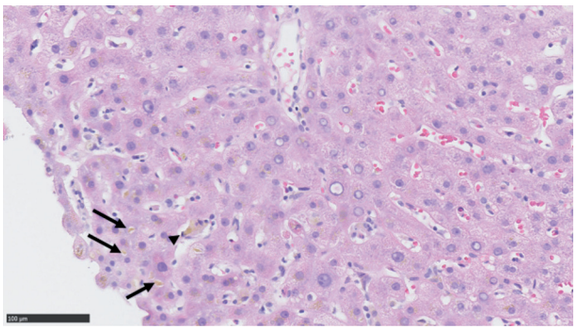

Figure 2.A. — The perivenular liver parenchyma shows intra-canalicular bilirubinostasis (arrow). Kupffer cells in the sinusoid contain bile pigments (arrow head). Apoptotic body and eosinophilic infiltration are also noticed. (H&E, x20 original magnification)

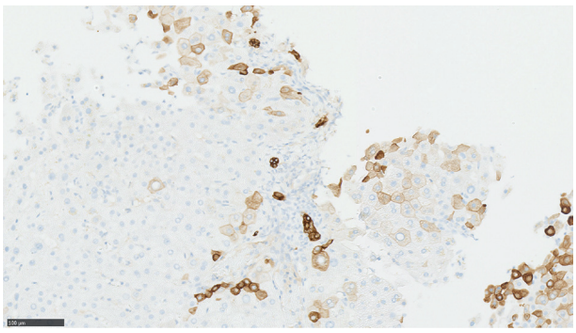

Figure 2.B. — Interlobular bile ducts show mild damage. Periportal hepatocytes show discrete K7 cytoplasmic positivity, which is considered as cholate stasis (Keratin 7 staining).

to Vaughan Williams' classification and is available only for intravenous administration due to its poor oral bioavailability. The current major use is unmasking Type 1 Brugada syndrome during electrophysiology testing. It has the capacity to accentuate the characteristic typical ST segment changes on electrocardiogram in these patients.(2,3)

Mechanisms of ajmaline-related cholestasis are unclear. Liver toxicity could be idiosyncratic mechanism as described with amoxicillin-clavulanate. Idiosyncratic liver toxicity depends on individual's susceptibility including polymorphisms of HLA subtypes.4 Moreover, Ajmaline is metabolized by the cytochrome p450 enzyme 2D6 which can be non-functional in some individuals. (5,6,7).

Few papers have described liver toxicity under chronic long-term administration of Ajmaline treatment for its antiarrythmic properties. (8,9,10,11) Only two authours described cholestasis induced by a single dose for Brugada diagnostic test. Liver biopsy was only performed by one author. (12,13)

There are strong evidences that our patient developed ajmaline linked liver toxicity. We didn't find any other drugs that could have induced cholestasis. Finally, we didn't stop any other drugs, liver enzymes normalized yet.

Ajmaline induced liver toxicity has to be considered in cases of unclear cholestatic hepatitis and extensive medical history of the patient needs to be explored. It is unclear whether or not biological tests are requested before ajmaline injection.

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