LETTER

A rare case of drug-induced liver injury caused by an epinephrine-autoinjector

Mohamed Barakat[1], M. Alfishawy[2], Kawser Ahmed[1], Suneetha Natarajan[1], Saphwat Eskaros[3]

(1) Departmant of Internal Medicine, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, Jamaica, NY ; (2) Division of Infectious Diseases, University of Pittsburgh Medical Center, PA ; (3) Departmant of Internal Medicine, Gastroenterology Division, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, Jamaica, NY

To the Editor,

Drug-induced liver injury (DILI) is the most common cause of acute liver failure in the USA. It is a diagnosis of exclusion based on history, physical examination, laboratory investigations and in some instances liver biopsy. Herein we present a case of a previously healthy young man who developed severe jaundice and elevated liver function tests [alanine transaminase (ALT) 700 U/L, aspartate transaminase (AST) 394 U/L, alkaline phosphatase (ALP) 636 U/L, gamma-glutamyl transpeptidase (GGT) 361 U/L, total bilirubin 26.67 mg/dL and conjugated bilirubin 16.05 mg/dL] after the inappropriate use of an epinephrine autoinjector. DILI was diagnosed after exclusion of all other possible causes. R value <2 suggestive of cholestatic liver injury, RUCAM score was 9 and consistent with high probability of DILI. Liver biopsy confirmed the diagnosis. Liver function tests returned to normal within several months. Sodium metabisulfite the preservative added to the epinephrine autoinjector has been reported to cause liver injury in an animal model. In the absence of any other medication, herbal preparation or supplements and the recent use of the epinephrine-autoinjector, sodium metabisulfite is the most likely cause of the patients DILI. Detailed history and investigations with the assistance of assessment tools led to the culprit. Preservatives and excipients used in medical preparations are not without harm and must be thoroughly evaluated in the right clinical context.

Case Presentation

A 35 year old man with no past medical history presented to the hospital for yellowish discoloration of the eyes. History revealed the use of an epinephrine autoinjector to treat an itchy erythematous rash three weeks prior to presentation and two days prior to the onset of his jaundice and pruritus. The patient did not take any other medication, illicit drugs, supplements or herbal preparations. There was no recent travel history or sick contacts. Physical examination revealed jaundice and a hyperpigmented patch on the back. Laboratory tests revealed alanine transaminase (ALT) 700 U/L, aspartate transaminase (AST) 394 U/L, alkaline phosphatase (ALP) 636 U/L, gamma-glutamyl transpeptidase (GGT) 361 U/L, total bilirubin 26.67 mg/dL and conjugated bilirubin 16.05 mg/dL. Prior liver function tests were normal. Hepatitis viral serologies, anti-nuclear antibodies (ANA) and anti-smooth muscle antibody (ASMA) were negative (Table 1). Liver ultrasound revealed abnormal echotexture of the liver suggestive of liver disease in the absence of biliary pathology. Liver biopsy showed cholestasis, aggregates of inflammatory cells (Fig. 1A), scattered ceroid-containing macrophages in the parenchyma (Fig. 1B) with activation of sinusoidal lining cells, bile duct plugs with severe panlobular acute cholestatic hepatitis, suggestive of DILI. Laboratory abnormalities normalized within 6 months without intervention.

Table 1. — **Viral serology performed to rule out viral hepatitis**

Viral serology	Result
HBsAg	Non-reactive
HBsAb	Reactive
HBcAb	Non-reactive
Anti-HCV core	Non-reactive
HEV antibody	Non-reactive
total	
HAV antibody	Reactive
total (IgG)	
HIV PCR	Non-reactive
EBV PCR	Non-reactive
CMV PCR	Non-reactive

Discussion

Patterns of DILI include hepatic, cholestatic and mixed features which are largely dependent on ratios of elevated transaminases to ALP. Non-genetic risk factors include age, sex, prior liver disease, alcohol consumption, HIV infection and diabetes (1). Assessment using the R

Correspondence to :Mohamed Barakat, Queens Hospital Center 82-68 164th St., 11432 Jamaica, NY, USA
E-mail : mohamed.barakat@mssm.edu

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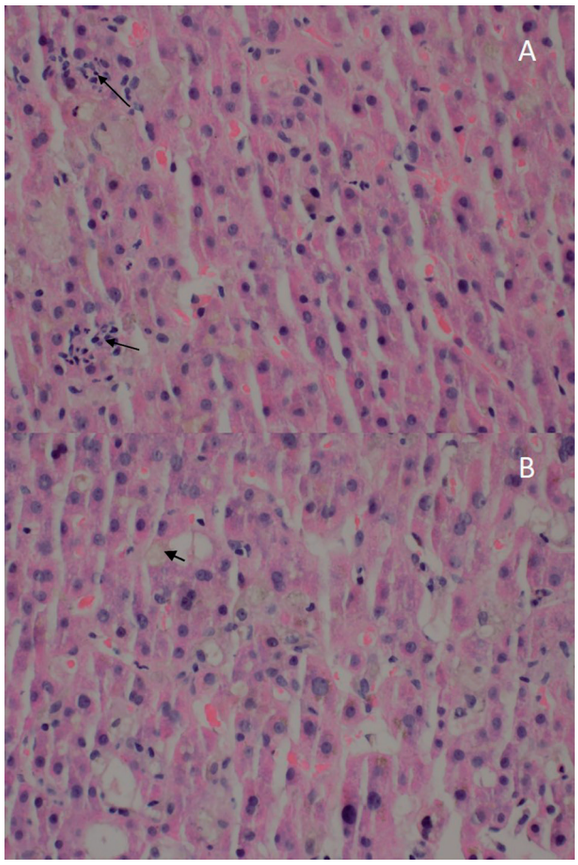

Figure 1. — A) Liver needle biopsy showing inflammatory cells, scattered mononuclear inflammatory cells with activation of sinusoidal lining cells. B) Liver needle biopsy showing ceroid containing macrophages.

value [ALT/Upper limit of normal(ULN) ÷ AP/ULN] is an essential tool to assess the pattern of hepatotoxic drug-induced injury; [hepatocellular (*R*>5), mixed (*R*=2-5), and cholestatic (*R*<2)]. Our patient's DILI had R <2 with marked elevation of ALP >2x ULN and similarly elevated ALT consistent with cholestatic injury.

The Roussel Uclaf Causality Assessment Method (RUCAM) scale is a diagnostic algorithm using a point based system that predicts the likelihood of a DILI (2). Elements of the scale are pattern of liver injury, time of onset of the event, latency period, times from drug withdrawal until reaction onset, risk factors, course of the reaction, concomitant therapy, exclusion of non-drug related causes, drug hepatotoxicity profile and rechallenge. The interpretation of the score is 0 or lower: excluded, 1-2 : unlikely, 3-5 : possible, 6-8 : probable, >8 : highly probable. In our case the RUCAM score was 9 points ; highly probable.

An epinephrine autoinjector is a medical device used to inject a measured dose of epinephrine using autoinjector technology. In addition to a pre-determined dose of epinephrine, autoinjectors contain a preservative; Sodium metabisulphite which prevents browning that can lead to a decrease in the effectiveness of epinephrine. Sulfites are known to cause allergic reactions in those with sulfite allergies (3), incidence has increased with the widespread use of sulfites. Reported reactions include contact dermatitis, when applied to the skin, asthma exacerbations when inhaled and anaphylaxis. In addition to their antioxidant effects, sulfites may oxidize into sulfite radicals (SO3-) which can lead to multi-organ harm. It has been shown that sulfite radicals initiate lipid peroxidation and inflammation in rat liver and kidney when ingested (4). This has been demonstrated through the measurement of Malondialdehyde levels which significantly increased in mice that were exposed to Sodium metabisulfite. Sulfites also induce an inflammatory response through the omega-6 inflammatory pathway in rat liver (5). The FDA mandates labeling prescription formulations to include a list of inactive ingredients due to an increase in adverse reactions associated with pharmaceutical excipients (6).

Conclusion

This case illustrates the importance of detailed history to determine the cause of DILI and the relevance of exploring potential adverse effects of preservatives and excipients in medical preparations.

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