

## Chronic Drug-Induced Liver Injury Induced by Amoxicillin-Clavulanate

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### Introduction

#### Chronic Drug-Induced Liver Injury

A 55-year-gentleman, presented to the National Liver Institute<sup>1</sup> hospital, Menoufia University, Egypt, with increasing jaundice and itching of 16 weeks duration. On presentation, the patient was conscious, jaundiced, with an average body built, acceptable vital signs and unremarkable cardiopulmonary examination. His medical history is significant for 15 year- diabetes mellitus and shift from oral hypoglycemic treatment to insulin in the last 5 years. He admitted habitual ingestion of tramadol, 25 to 50 mg per day for 10 years.

The condition started 10 days after completing a one week course of amoxicillin-clavulanate 2 grams per day plus ibuprofen 400 mg twice daily post tooth extraction. The early biochemical investigations denoted cholestatic hepatitis with the canalicular enzymes disproportionately higher than the hepatic transaminases. Abdominal sonography and Magnetic Resonance Cholangiopancreatography (MRCP) were negating either obstruction or masses.

The repeated investigations after hospitalization showed remaining cholestatic elements as hyperbilirubinemia and persistently elevated canalicular enzymes. A second abdominal sonography with dedicated doppler study and MRCP showed hepatosplenomegaly, a rim of ascites and normal pancreaticobiliary system. Further laboratory investigations indicated negative serological markers for viral, autoimmune hepatitis aetiologies as well as for bacterial sepsis or Wilson's disease.

Histopathological examination of the liver biopsy showed features of chronic hepatitis and cholestasis with residual features of acute hepatitic injury. The biopsy indicated moderate expansion of the portal tracts, by both acute and chronic inflammatory cells mainly of neutrophils (**Figure 1**) with a mild degree of lobular inflammation (**Figure 1**). The partially disturbed lobular architecture by Porto-portal fibrous links had reflected a mild degree of fibrosis (**Figure 2**). The microvesicular steatosis (**Figure 3**) with the associated massive portal eosinophilic infiltrates (**Figure 4**) were supportive for the diagnosis of the drug-related liver injury. The Intra canalicular cholestasis, cholestatic rosette formation (**Figure 5**), ductular proliferations along with biliary interface were remarkably impressive of chronic cholestasis.

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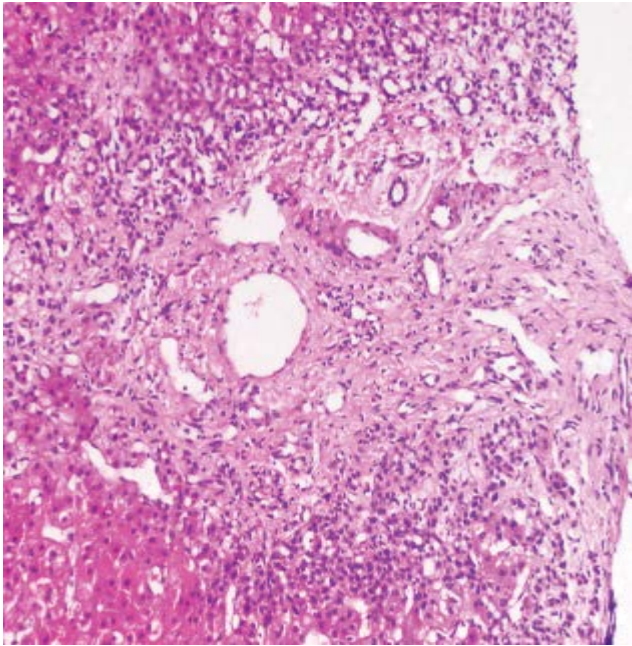
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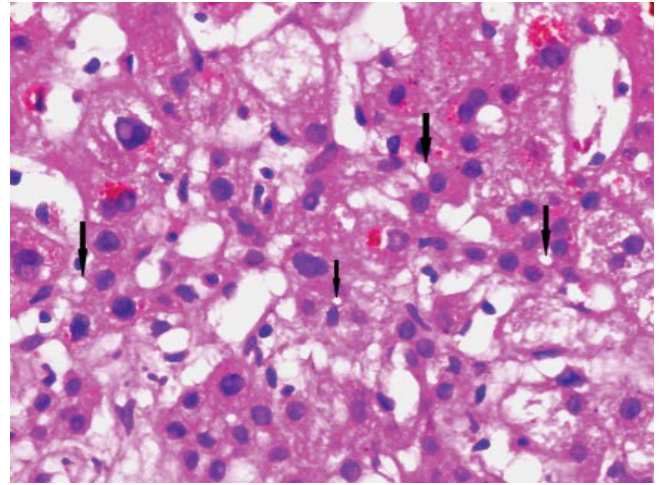
The Russel Uclaf causality assessment method (RUCAM) score was highly probable (+8) substantiating the potentiality of Drug-Induced Liver Injury (DILI). Initiation of prednisolone 60 mg daily was shortly followed by the disappearance of the rim of ascites and regression of the biochemical abnormalities as well as itching. Two weeks later, the biochemical hepatic parameters showed a further significant reduction. This case is representative to the idiosyncratic liver injuries related to amoxicillin-clavulanate in a patient with the susceptible genetic milieu.

Learning points:

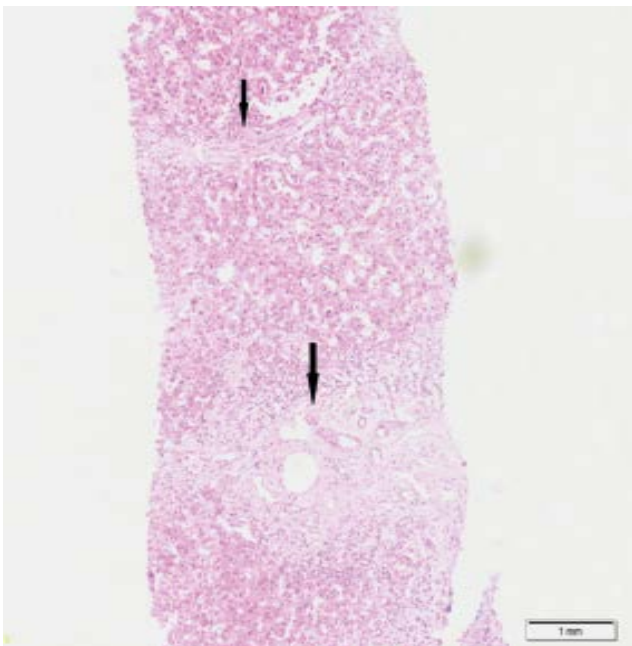
- The liver injury associated with amoxicillin-clavulanate is a mostly cholestatic type, although, hepatocellular or mixed liver injury can happen.



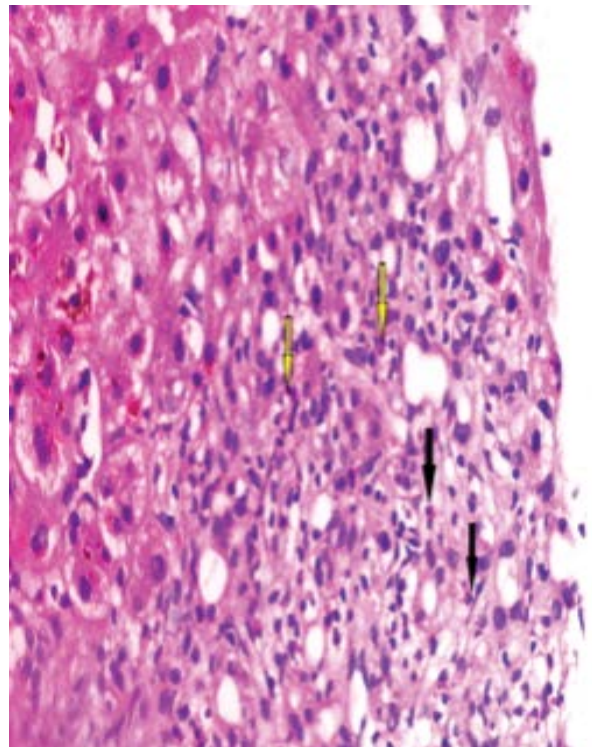
**Figure 1** Chronic inflammatory cells mainly of neutrophils.



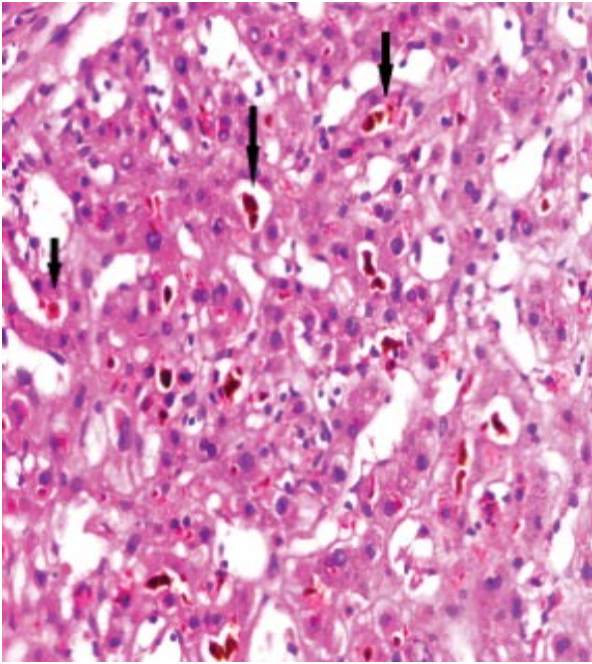
**Figure 3** The microvesicular steatosis.



**Figure 2** The partially disturbed lobular architecture by Porto-portal fibrous links had reflected a mild degree of fibrosis.



**Figure 4** Massive portal eosinophilic infiltrates.



**Figure 5** The Intra canalicular cholestasis, cholestatic rosette formation.

- Clinically recognizable liver injury due to ibuprofen is very rare with a reported rate of 1.0-1.6 cases per 100,000 prescriptions.
- Opioids like drugs are rare causes of drug-induced liver disease and are not mentioned in case series of clinically apparent liver injury.
- Drug-induced chronic cholestasis histologically resembles other causes of chronic cholestasis, such as primary biliary cholangitis, biliary obstruction, or primary sclerosing cholangitis
- A small percentage of patients with drug-induced cholestasis continue to have the cholestatic injury and may develop secondary biliary cholangitis/cirrhosis.
- The latest drug introduced into a patient who is taking various medications is the most likely to be the injury related offender.