



Amoxicillin-clavulanate-induced Granulomatous Hepatitis: Case Report and Review of the Literature

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Abstract

Amoxicillin-clavulanate (AC) is a common cause of drug-induced liver injury, either cholestatic or mixed with hepatitis pattern. Rarely, AC causes granulomatous hepatitis. We report a new case of AC-induced granulomatous hepatitis documented by liver biopsy, with complete resolution of any histological sequelae on a follow-up liver biopsy after AC was withdrawn.

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Introduction

Amoxicillin-clavulanate (AC) is identified as a common cause of nonacetaminophen drug-induced liver injury (DILI)^{1,2} as well as the consequent hospitalizations for adverse hepatic reactions.² The Drug-Induced Liver Injury Network (DILIN) cohort was established in 2004 in the USA and currently consists of over 1450 cases of DILI, of which 11% are due to AC. Classically, AC-DILI presents as a spectrum of cholestatic liver injury, with pure intra-hepatic cholestasis and/or mixed hepatic/cholestatic injury, but there are only rare reports of a granulomatous hepatitis (GH) pattern.^{3–5} Our case demonstrates GH caused by AC-DILI, with a follow-up complete resolution of the histological lesion once the drug was withdrawn.

Case report

A 58-year-old woman with a history of polysubstance abuse (alcohol, methamphetamine, cocaine, and marijuana) presented with 1-week history of epigastric discomfort, malaise, and nausea with dark urine and pale colored stools, following a 7-day course of AC for Bartholin abscess. She denied any recent travel or intravenous drug use. She was afebrile and hemodynamically stable on presentation. Physical exam was significant for scleral icterus and epigastric tenderness but no

rebound tenderness. Initial laboratory examination revealed elevated total bilirubin at 3.2 mg/dL, alkaline phosphatase at 510 IU/L, alanine aminotransferase at 388 IU/L, and aspartate aminotransferase at 171 IU/L. Lipase level, international normalized ratio, and platelet count were within normal limits. Total leukocyte count was also normal at 6.6 (1000/ μ L) but differential count showed eosinophilia (8.3%), which trended up to 12% with absolute eosinophil count of 0.76 (1000/ μ L). The liver enzymes and bilirubin trend throughout the hospitalization is shown in Fig. 1. International normalized ratio continued to be within normal range throughout the hospitalization.

Computed tomography of the abdomen showed normal liver with a low-density lesion in the right lobe of the liver, probably representing a cyst. Magnetic resonance imaging of the abdomen showed heterogeneous arterial enhancement of the liver without biliary obstruction. Serological work-up, including testing for human immunodeficiency virus, rapid plasma reagin, hepatitis panel (hepatitis A antibody subtype IgM, hepatitis surface antigen, hepatitis B core IgM, hepatitis C antibody), antineutrophilic antibody, antimitochondrial antibody, and anti-smooth muscle antibody, was negative. Ceruloplasmin, ferritin, and immunoglobulin panel were normal. Urine drug screen was positive for cannabinoids. Acetaminophen level was negative at presentation.

Liver biopsy showed portal granulomas centered around the bile ducts, with a significant biliary epithelial injury. Fungal, acid-fast bacilli and Giemsa stainings were negative, and no fibrosis or periportal copper deposition was seen to suggest chronic cholestatic disease. Abundant eosinophils with mononuclear cells were observed. Cytokeratin 19 showed increased biliary profiles in some portal tracts. However, there was an absence of marginal ductular reaction or ductopenia. PAX-5 staining did not show any B cell aggregates (Fig. 2). Other differential diagnosis considered (and ruled out) included primary biliary cholangitis, sarcoidosis, Hodgkin's disease, and Langerhans cell histiocytosis. It was not clear if the granuloma in the liver biopsy was pre-existing undiagnosed or related to the use of AC.

Follow-up at 1 month showed continuous improvement in the liver enzymes, but they did not normalize. Four months later, the liver panel showed a total bilirubin of 1.2 mg/dL, aspartate aminotransferase of 43 IU/L, alanine aminotransferase of 104 IU/L, and alkaline phosphatase of 249 IU/L. A repeat liver biopsy was performed at 6 months and showed nearly normal liver parenchyma, with no granulomas, fibrosis, steatohepatitis, steatosis, fibrosis or cirrhosis, (evaluated with trichrome and reticulin stainings) along with intact bile ducts (Fig. 3). Eventually, at 7 months, her liver enzymes

Keywords: Granulomatous hepatitis; Amoxicillin; Clavulanate; Drug-induced liver injury; Liver biopsy.

Abbreviations: AC, amoxicillin-clavulanate; DILI, drug-induced liver injury; GH, granulomatous hepatitis; HLA, human leukocyte antigen.

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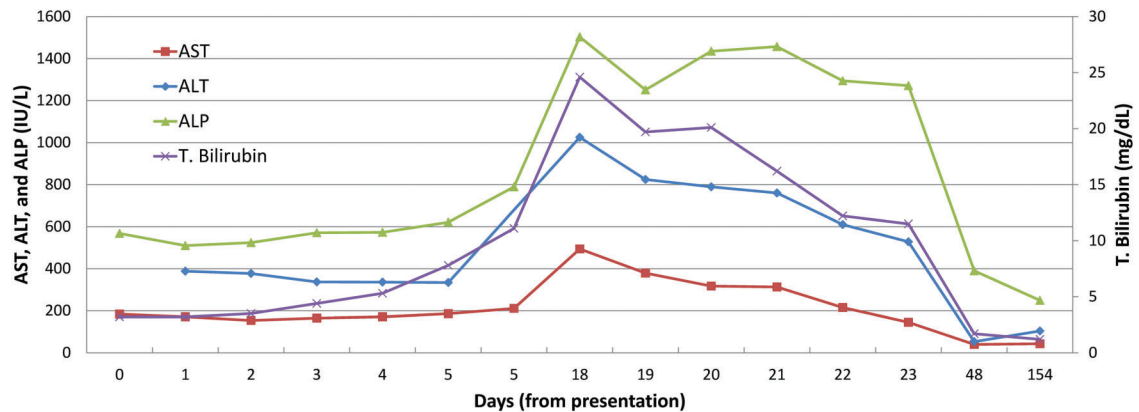


Fig. 1. Liver panel trend throughout the course of liver injury.

Abbreviations: T. Bilirubin, total bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

normalized completely. This strongly suggested that her granulomas had been induced by the AC, and they were found to be completely resolved in the follow-up liver biopsy.

Discussion

AC is an antibiotic combination consisting of amoxicillin, a third-generation penicillin and a beta-lactam clavulanate that acts against beta-lactamase producing penicillin-resistant bacteria. AC is one of the most common antibiotic regimens prescribed in the USA and is available in various dose

combinations of 250 to 875 mg amoxicillin with 125 mg of clavulanate, taken 2–3 times a day. AC is currently the most common cause of nonacetaminophen DILI in the USA and Spain.^{1,2} Injury onset is reported within a few days to up to 8 weeks after therapy initiation and can also occur after a delay of days to up to 6 weeks after completion of the antibiotic course.

Hepatotoxicity is typically characterized by a cholestatic pattern with marked elevations in alkaline phosphatase and gamma-glutamyltranspeptidase but a mixed or hepatocellular pattern has been reported as well, particularly in younger

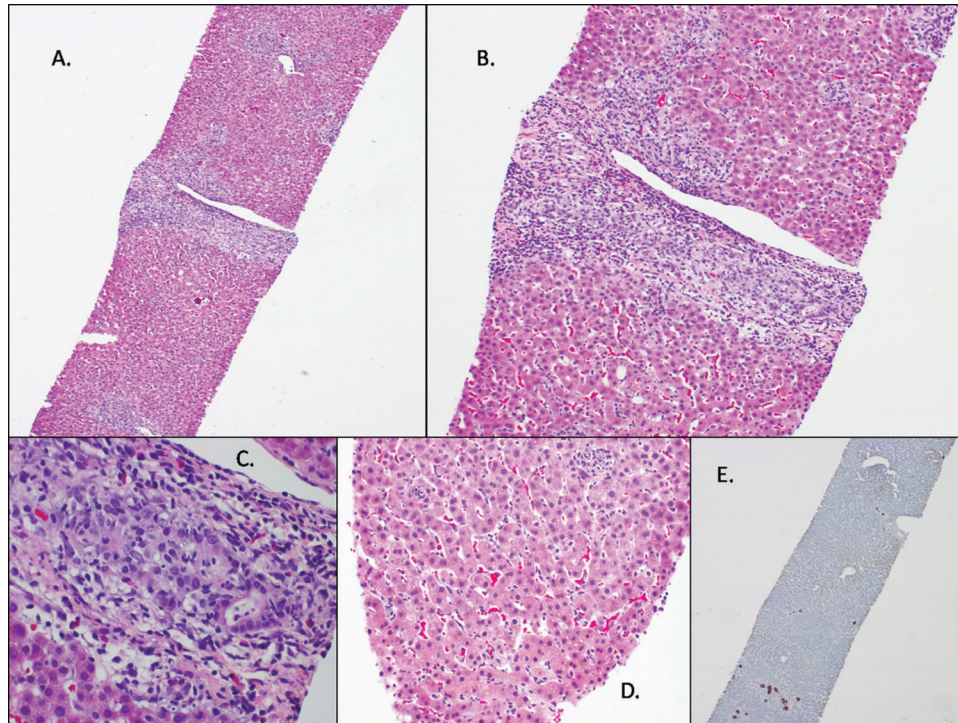


Fig. 2. All portal tracts were expanded by mononuclear inflammatory infiltrate. A, H&E staining (x40). B-C, Bile ducts in multiple portal tracts showed epithelioid granulomata centered on the bile duct (B, H&E, B, x100; C, x200). D, Marginal ductular reaction was only mild and focal; foci of lobular inflammation, including sinusoidal infiltrate (D, H&E, x200) and endothelitis (not shown) were observed. E, There was no ductopenia and at least a portion of the bile duct in each portal tract was consistently preserved, as shown by immunostain for cytokeratin 7 (x40).

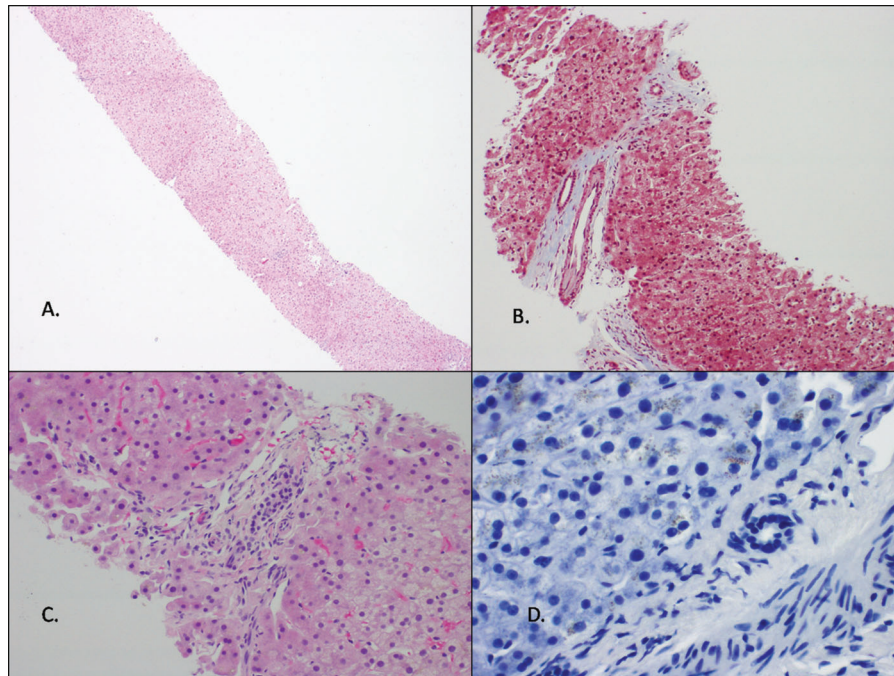


Fig. 3. Complete resolution of inflammation. A-B, Nearly normal liver parenchyma (A) and no fibrosis (B) were observed. C, The bile ducts were intact, without any evidence of persistent injury. D, A single focus of periportal copper deposition and focal hepatocyte cholestasis were identified, which will likely be resorbed in due course of time (rhodanine stain, x400).

patients.⁶ The hepatic injury is estimated to occur in 1 out of 2500 prescriptions and to be more common in men, the elderly, and after multiple courses.^{3,7} A genetic predisposition with human leukocyte antigen (HLA) type has also been identified, with a significant association of the HLA class II haplotype DRB1*1501-DRB5*0101-DQB1*0602 with the susceptibility to AC-associated hepatotoxicity.⁸

The exact mechanism of hepatotoxicity is unknown but an immune-allergic reaction to the clavulanate component (rather than amoxicillin) is proposed. Initial presenting symptoms include fatigue, nausea, and abdominal pain, followed by pruritus and jaundice, except in children, where the injury is typically anicteric. Immune-allergic manifestations, like fever, rash and eosinophilia, are not always present. The antineutrophilic and antimicrobial antibody have been reported in 18% and 15% of cases, respectively.³ Granulomatous injury, especially when associated with eosinophilia suggests a hypersensitivity immune-allergic phenomenon. Hepatic injury can be severe and prolonged (4–24 weeks) but rarely results in lasting injury or death. In the largest study of AC-DILI, with 117 cases, only 12 (11%) continued to have ongoing evidence of liver injury at 6 months after the onset and to have developed chronic DILI, and 5 of those normalized aminotransferases in 2–3 years.³

The most common causes of granulomatous liver disease include sarcoidosis, primary biliary cirrhosis, and tuberculosis.⁹ Numerous drugs have been implicated in the development of GH. In a retrospective review of 88 cases of GH at Mayo Clinic, comprehensive work-up for etiology revealed idiopathic GH confined to the liver in 50%, sarcoidosis with the confirmed extra-hepatic disease in 22%, drug-related GH in 6%, tuberculosis in 3%, and other causes in 19%.¹⁰

In a more recent single-center report, hepatic granulomas were found in 2–15% of unselected liver biopsies and out of these, autoimmune liver diseases (primary biliary cirrhosis, overlap syndrome, and autoimmune hepatitis) accounted for the majority of cases (68%), followed by sarcoidosis (7.5%), chronic hepatitis B virus and hepatitis C virus infection (7.5%), idiopathic (6%), drugs (3%), and other miscellaneous causes (7.5%).¹¹ Numerous medications, like phenylbutazone, allopurinol, sulfonamides, phenytoin, carbamazepine, chlorpropamide, quinidine, methyl dopa, nitrofurantoin, isoniazid, amiodarone, and diazepam, have been linked to hepatic granulomas. In a large study with 117 patients with confirmed AC-DILI, histopathology was available for 32, most of which showed cholestatic patterns of injury. There were eosinophils and granulomas noted in 21 and 28 cases, respectively; only 4 cases showed large epithelioid granulomas and none of the cases were classified as GH.³ GH due to AC-DILI was reported the first time by Silvain *et al.*⁴ but no follow-up liver biopsy was available after normalization of liver enzymes over 75 days. In another case series of 15 patients with AC-DILI, confirmed histology was available for 7 patients only and out of those only 1 had features of GH on initial biopsy.⁵ GH pattern of AC-DILI is unusual and only reported in a few reports in the literature.^{3–5}

Our case demonstrated classical findings of GH on liver histology and a clear temporal relation of these findings to abnormal aminotransferases and AC intake. After 6 months, the aminotransferases markedly improved but did not normalize completely; therefore, a repeat biopsy was performed. It showed a complete histological resolution of GH, establishing this case as being an unusual pattern of AC-induced liver injury. To our knowledge, this is the first case of AC GH that has a follow-up liver biopsy confirming the resolution of GH.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception, design, and drafting of the manuscript (AA), manuscript preparation with substantial contributions to intellectual content (NJ, RJ), critical editing and revisions of the manuscript (HE).

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