Acute Cholestatic Hepatitis Due To Clarithromycin: Complete Resolution Of A Usually Progressive Disease On Drug Withdrawal

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Citation

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Abstract

Clarithromycin is a macrolide antibiotic commonly indicated for use in upper and lower respiratory infections and has a well established safety and efficacy profile. Rare case reports of fatal progressive cholestatic and fulminant hepatitis from clarithromycin have been described but the spectrum of liver disease and its characteristics are not well defined. We describe a case of clarithromycin-induced liver injury notable for the combination of cholestasis with associated lobular hepatitis and complete resolution of symptoms on withdrawal.
Health care providers should be aware of a rare idiosyncratic cholestatic hepatitis caused by this drug which may require immediate discontinuation and careful monitoring.

INTRODUCTION

Clarithromycin (Biaxin, Abbott laboratories, North Chicago, IL) is a commonly prescribed macrolide antibiotic for upper and lower respiratory infections. Mild and sometimes symptomatic hepatitis is common especially in elderly population taking the antibiotic in high dose ([1]). However, serious side effects are rare and include progressive cholestatic hepatitis ([2], [3]) and fulminant hepatic failure ([4], [5]). We describe a case report of clarithromycin induced cholestatic hepatitis which completely resolved over a several week period upon withdrawal of the drug.

CASE REPORT

A 48-year-old Caucasian female was admitted with 2 week history of jaundice & dark discoloration of her urine. The patient was previously diagnosed with right breast cancer five years prior and subsequently underwent right mastectomy (T1N1M0) followed by chemotherapy and radiation therapy. Tamoxifen was prescribed to prevent recurrence. Three years later, she presented with bone metastasis. She was treated with chemotherapy comprising of 5 cycles of taxol, carboplatin and herceptin. Three weeks later, she presented with cough, shortness of breath and chest x-ray findings of an infiltrate. At this time there was no jaundice, icterus or pruritus. Bilirubin and alkaline phosphatase were normal. Aminotransferases were less than 2 times the upper limit of normal. She was treated for pneumonia with 1 week course of levofloxacin without any improvements. Subsequent blood cultures grew Mycobacterium abscessus, for which she was treated with intravenous antibiotics including imipenem, amikacin, cefoxitin and clarithromycin. Two weeks after beginning this regimen the patient noted jaundice and pruritus and returned for evaluation.

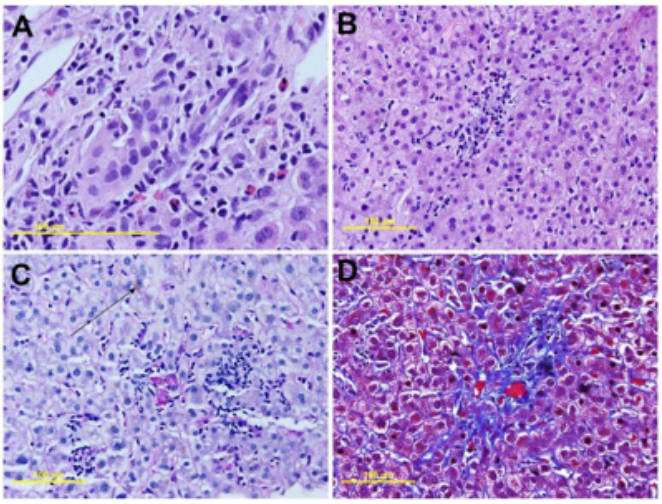
Past medical history was significant only as noted above. She had no prior history of liver disease and she did not drink alcohol. On examination, she appeared icteric. Neck veins were not distended. There were no stigmata of chronic liver disease. Abdomen was nondistended, soft with mild tenderness in the right upper quadrant. There was no free fluid or hepatosplenomegaly. Extremities did not show peripheral edema.

Complete blood counts showed peripheral eosinophilia. Liver enzymes showed a cholestatic picture with an elevated alkaline phosphatase of 311 U/L and a primarily conjugated hyperbilirubinemia peaking at 6.9 mg/dl. ALT was 112 U/L and AST was 110 U/L. Acute hepatitis A antibody-IgM, hepatitis B surface antigen and hepatitis B core antibody-IgM were non-reactive. Antibody for hepatitis C virus (HCV) was reactive; however HCV RNA by PCR was negative twice over the preceding 12 months period. Antibody to the human immunodeficiency virus (HIV) was

also negative. Anti-mitochondrial antibody (AMA) was negative. Ultrasound of the liver and gall bladder did not reveal any evidence of intra or extra-hepatic biliary dilatation. CT of the abdomen was unremarkable. A percutaneous liver biopsy revealed acute lobular inflammation with lymphocytes and few eosinophils along with intrahepatic cholestasis (Fig. 1).

Figure 1

Figure 1: Liver Histology: A. Infiltration of a portal tract, by lymphocytes and a few eosinophils, and lymphocytic infiltration of the epithelium of a bile duct. B. Infiltration by lymphocytes in a portal tract, and the lobular parenchyma, with swelling of hepatocytes, and mild lobular disarray. C. A focus of Kupffer cell clustering, containing PAS-positive membrane debris and intrahepatic cholestasis (black arrow). D. Staining for collagen showing mild pericellular fibrosis. A and B, hematoxylin & eosin stain; C, PAS stain with diastase; D, Masson's trichrome stain.

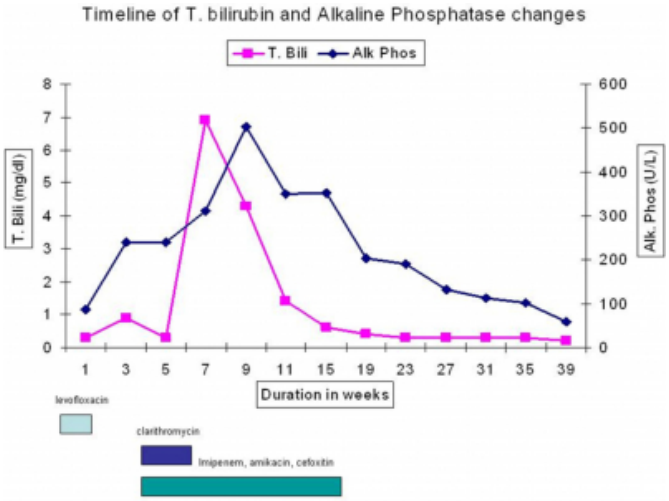


There were no granulomas and acid fast stain for Mycobacterium tuberculi was negative (not shown). The findings of cholestasis without obstruction, presence of eosinophils and lobular inflammation suggested drug toxicity.

The patient had been on number of antibiotics recently including clarithromycin, amikacin and cefoxitin; however clarithromycin was felt to be the likely inciting agent as the patient's clinical course of acute jaundice appeared to closely correlate with the use of this antibiotic. Clarithromycin was stopped and other medications including cefoxitin and amikacin were continued. Upon discontinuation of the clarithromycin there was a rapid decline of bilirubin and alkaline phosphatase over the first 3 weeks followed by a continued slower decline to normal values over the next 28 weeks (Fig. 2).

Figure 2

Figure 2: Association of drug ingestion and jaundice: A timeline of changes in bilirubin and alkaline phosphatase in this patient. The bars at the bottom of the graph show duration of exposure to potential drugs causing cholestasis. Decline in liver enzymes was prompt but sustained upon withdrawal of clarithomycin.



DISCUSSION

Cholestasis, defined as impairment of bile flow or production, is a well- recognized presentation of drug induced liver disease. Drugs account for 17-20% of the cases of cholestatic hepatitis ([6]). According to the criteria generated by an International Consensus Meeting in 1990 for drug-induced hepatotoxicity, a history of inciting drug intake within 90 days of reaction followed by more than 50% decline in cholestasis within 180 days of withdrawal is suggestive of drug toxicity ([7]). The most likely explanation of our patient's symptoms is drug toxicity. Presence of peripheral eosinophilia and liver biopsy findings in this case support a diagnosis of drug induced cholestatic liver disease. Although the patient was on multiple drugs, had an ongoing mycobacterial infection and had some evidence of mild liver dysfunction prior to beginning clarithromycin, the timeline of the development of the acute jaundice and the significant elevations in aminotransferases and alkaline phosphatase closely correlated with the duration of clarithromycin use. Liver enzymes nearly normalized in the ensuing months following withdrawal of clarithromycin while other medications were continued.

The differential diagnosis of acute cholestatic liver disease includes (but not limited to) acute viral hepatitis, drug reactions and biliary obstruction. Acute viral hepatitis was ruled out by negative serologies. Biliary obstruction due to

stones or masses was excluded by a normal appearing ultrasound of the bile duct. Other less likely diagnostic possibilities such as acute alcoholic hepatitis was excluded based on absence of such history. Benign recurrent intrahepatic cholestasis is unlikely as it usually presents at a young age and the patient failed to give any prior history of jaundice. There was no evidence of metastasis from the recurrent breast cancer on the CT scan of abdomen. Granulomatous liver diseases such as mycobacterial infection, sarcoidosis and lymphoma were also excluded by the absence of granulomas on biopsy and negative AFB stains.

Clarithromycin is a commonly prescribed macrolide antibiotic with a well established safety profile. Clarithromycin however has been associated with rare cases of progressive cholestatic hepatitis and fulminant hepatic failure. Yew et al described a similar case report of cholestatic hepatitis induced by clarithromycin therapy in a patient with Mycobacterium chelonae lung infection ([8]). While serious and fatal reactions are rare, they do occur. Fox et al described a case of a 59-year-old female who was prescribed clarithromycin for acute maxillary sinusitis and developed a progressive form of cholestatic hepatitis and renal failure and eventually expired. Her liver biopsy demonstrated moderate hepatocellular cholestasis and eosinophilic infiltrates ([3]). Shaheen et al reported a case of a 25-year-old male who was prescribed clarithromycin for sinusitis, subsequently developed liver failure, and eventually required a liver transplant. This patient had also been taking acetoaminophen in high therapeutic doses and this might have contributed to the severity of his disease ([5]). Another case of fulminant hepatic failure was described in a 58-year- old female who was prescribed clarithromycin for pneumonia. Fortunately, this latter patient recovered 10 days later without requiring liver transplant ([4]). However, yet another case of fulminant hepatic failure in a 40-year-old female resulted in death ([9]). A more recent description of severe cholestasis in a 15-year-old girl who had taken clarithromycin and nimesulide suggested that prolonged used of corticosteroids might be beneficial ([2]). This was not a viable option in our case in view of active mycobacterial bacteremia. Our patient was on a number of other antibiotics for the treatment of mycobacterium abscessus, it is possible that drug interactions might potentially have resulted in increased hepatic toxicity from clarithromycin. The case highlights the fact that early recognition of this drug-induced hepatotoxicity and withdrawal of clarithromycin may reverse a potentially fatal complication.

In conclusion, we describe a case of cholestatic hepatitis which had classical clinical, biochemical and histological features of a rare and usually progressive drug-induced hepatitis (in this case clarithromycin) which improved on withdrawal of the drug. This suggesting that early discontinuation may prevent the progression to a more serious liver disease. Clinicians need to be aware of this potential complication of this widely prescribed and generally well- tolerated antibiotic.

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