A CASE REPORT

Acute Liver Failure Secondary to Clarithromycin. A Case Report and a Literature Review

by Hassan Albataineh and Firdous Siddiqui

Acute liver failure (ALF) is defined by the presence of hepatic encephalopathy occurring as a consequence of severe liver damage in patients without previous, clinically overt liver disease. It can result from a wide variety of causes, of which drug-induced or viral hepatitis are the most common. Four cases of ALF due to clarithromycin have been reported thus far. Herein, we report a case of ALF secondary to clarithromycin in a patient with alcoholic liver disease who was being treated for pneumonia.

INTRODUCTION

Acute liver failure (ALF) refers to the rapid development of a severe acute liver injury with jaundice, encephalopathy and impaired synthetic function in a person who previously had a normal liver or a well compensated liver disease (1). In the United States, acute viral hepatitis accounts for approximately 50% of cases, whereas acetaminophen toxicity accounts for approximately 20%–35% of cases. Other causes are drug-induced hepatitis, alcoholic hepatitis, autoimmune hepatitis, Wilson’s disease, acute fatty liver of pregnancy, congestive heart failure and ischemic hepatitis. ALF can be fatal and thus prognosis is variable. Spontaneous recovery is more likely with lower grades of encephalopathy. Sixty-five percent to 70% of patients with grade I to II encephalopathy, 40% to 50% with grade III encephalopathy and less than 20% with grade IV encephalopathy recover. The only therapy proven to improve patient outcome in ALF is orthotopic liver transplantation (1).

Clarithromycin is a widely prescribed macrolide antibiotic for respiratory, disseminated mycobacterial, skin and helicobacter pylori infections. It is relatively a safe drug. Hepatic dysfunction, including increased liver enzymes (less than 1%), and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible (2). To our knowledge, there are four reported cases of clarithromycin induced fulminant hepatic failure (FHF). We report the fifth case of FHF secondary to clarithromycin.

CASE REPORT

A 39-year-old African American male presented to the emergency room with productive cough, dyspnea, pleuritic chest pain, fever and chills. Chest x-ray
showed left upper lobe infiltration, consistent with community acquired pneumonia. On arrival he was alert and oriented to time, place and person. No stigmata of chronic liver disease were noted on physical exam. Alanine aminotransferase (ALT) level was 23 and Aspartate aminotransferase (AST) was 143. Patient was admitted and was started on clarithromycin 500 mg orally twice a day and ceftriaxone 1 gram intravenously once a day. The following day, he developed right upper quadrant pain, recurrent emesis and confusion. Laboratory tests revealed elevated ALT and AST of 1700 and 2600 respectively, which progressively increased over the next two days (Figure 1). Alkaline phosphatase, bilirubin and ammonia level were normal. Albumin was 3.3, PT 22, INR 2.1 and PTT 32. On physical examination, he was sleepy but arousable, markedly confused, incoherent, with asterixis consistent with grade III encephalopathy. Patient's temperature was 103 degrees Fahrenheit, however, the other vital signs were stable. There was no icterus, no Kayser-Fleischer rings or signs of volume overload. He had tender hepatomegaly with liver span of 20 cm. There was rebound tenderness but no guarding. Spleen was normal in size and there was no evidence of ascites. Bowel sounds were normal. There were no focal neurological deficits. Other medical problems were congestive heart failure with EF 10%, hypertension and alcohol abuse (1 pint of hard liquor a day). The home medications were digoxin, furosemide, spironolactone, metoprolol and quinapril, which were all continued in the hospital.

The patient was diagnosed with acute liver failure and transferred to medical intensive care unit, where gastroenterology service was consulted. He was treated with intravenous fluids, lactulose, and vitamin K. Liver transplant was considered. Other causes of ALF were excluded, he had negative antibodies to hepatitis A, B and C, antinuclear, smooth muscle, HIV, negative hepatitis B antigen, acetaminophen level <10, ceruloplasmin 48, negative blood culture and abdomen US showed diffuse fatty liver infiltrate with hepatomegaly of 20 cm.

After excluding other causes of ALF, clarithromycin and ceftriaxone were discontinued. Shortly after that, his clinical condition had improved, abdominal pain and emesis had stopped and he became fully alert and oriented. Liver enzymes showed gradual improvement for the following three days; ALT decreased to 3100 then to 1100 then to 330 and AST decreased to 2700 then to 1800 then to 48 (Figure 1). That improvement made the liver transplant unnecessary. The patient declined liver biopsy and he left the hospital against medical advice.

DISCUSSION
Our patient developed ALF After starting clarithromycin and ceftriaxone. Other causes of ALF were excluded by normal or negative appropriate diagnostic means. Although ceftriaxone is known to cause slight elevation of liver enzymes in 3% of the patients, there are no reported cases of ALF caused by this drug. It was deduced that none of the concomitant medications were the cause of ALF in this patient because he started taking them a long time prior to the development of the condition, which resolved while he was still taking them.

Alcoholic hepatitis is a common cause of ALF. In our patient, his AST:ALT ratio on presentation was more than 5:1, which is consistent with alcoholic hepatitis. But this patient was well compensated upon his presentation and he developed ALF in the hospital where he did not consume any alcohol. Although alcohol was not the major etiology of ALF in this patient, it had a major contribution to its development.

Congestive heart failure (CHF) is another cause of FHF. Our patient, who has CHF with EF 10%, was well compensated with no symptoms or signs of volume overload.

FHF in our patient was considered to be secondary to clarithromycin because of the relation between liver enzymes to starting and discontinuing the medication. Refer to graph. Another possibility is that a combination of clarithromycin and ceftriaxone had caused ALF in this patient who had alcoholic liver disease.

There are four reported cases of ALF associated with clarithromycin. The first case was a 25-year-old male, previously healthy and social alcohol drinker. He developed ALF nine days after starting clarithromycin 500 mg orally twice a day for sinusitis. Five days later, he developed stage III encephalopathy. He underwent orthotrophic liver transplantation. Postoperatively, he
developed intracranial hemorrhage (3). The second case was a 40-year-old female, with a history of end-stage renal disease on hemodialysis, not alcoholic. She developed ALF seven days after starting clarithromycin 500 mg orally twice a day for upper respiratory infection. She developed respiratory failure and passed away 13 days after developing ALF (4). The third case was a 47-year-old male, with history of chronic alcoholism and treatment with disulfiram. He developed ALF and Lyell disease seven days after starting clarithromycin 500 mg orally twice a day for fever, odinophagia and myalgias. Subsequently, he developed septic shock and died (5). The fourth case was a 58-year-old female, social alcohol drinker, with a history of hypertension. She developed ALF four days after taking two doses of clarithromycin 500 mg orally for pneumonia. Clarithromycin was discontinued and she received supportive care. She was discharged from the hospital 20 days after admission in good clinical condition. Subsequently, her liver values had completely normalized (6).

ALF is a fatal disease. Determining the etiology and withdrawing the offensive agent play a vital role in management. clarithromycin should be considered as a potential cause and should be discontinued promptly in patients developing ALF.

References
2. Biaxin prescribing information at WWW.BIAXIN.COM