CASE SERIES

Amiodarone Induced Liver Cirrhosis. Report of two cases

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Abstract

Amiodarone is used commonly in patients with cardiac diseases. Common side effects include thyroid dysfunction and hepatic abnormalities. However, recently there has been concern for developing liver cirrhosis secondary to amiodarone therapy. We present two cases of liver cirrhosis in patients taking amiodarone. Their clinical presentation as well as histological features are discussed in detail.

Introduction

Amiodarone is commonly used to treat cardiac tachyarrhythmias in elderly patients. Many patients receive this therapy for a prolonged period of time. Asymptomatic elevation of serum aminotransferases occurs in 25% of those treated while symptomatic hepatic dysfunction occurs in less than 1% [1]. Cirrhosis, however, is a rare complication of chronic oral amiodarone therapy [2]. The cause of amiodarone induced hepatic injury is not entirely clear. Immunologic mechanisms are suspected in instances of acute hepatitis associated with a positive direct Coombs test [3]. Chronic liver injury resulting from the long half-life of amiodarone may result in lesions of varying nature, including steatosis that resembles alcoholic liver disease, or phospholipidosis [4-6]. We report the clinical and histologic features of two patients with amiodarone induced liver cirrhosis.

Case presentation

Case 1

A 72 year old Caucasian gentleman with diabetes, hypertension, and chronic kidney disease was admitted with generalized fatigue and worsening ascites. His diabetes was reportedly well controlled. He had no history of alcohol intake. Pertinent medications included amiodarone at 200 mg per day, simvastatin and glipizide. He had been taking simvastatin for several years. However the amiodarone had been started three years ago. Initial laboratory tests were as follows: bilirubin 1.9 mg/dL, aspartate amino transaminase 106 IU/L, alanine amino transaminase 75 IU/L, alkaline phosphatase 147 IU/L, prothrombin time of 20 seconds. An ultrasound of the liver with Doppler showed a nodular contour consistent with cirrhosis, splenomegaly and massive ascites. Serologic studies were negative for chronic viral hepatitis. There was also no clinical or laboratory evidence of autoimmune hepatitis, Wilson's disease, or hemochromatosis. A liver biopsy was performed, which showed steatohepatitis with a striking amount of Mallory hyaline within the hepatocytes, and an associated neutrophilic infiltrate, consistent with amiodarone toxicity (Fig. 1). The patient died during his hospitalization secondary to complications from his liver disease.

Case 2

The second patient was a 67-year-old African-American woman with a history of coronary artery disease, congestive heart failure requiring AICD placement, who was transferred from an outside facility for increasing confusion. There

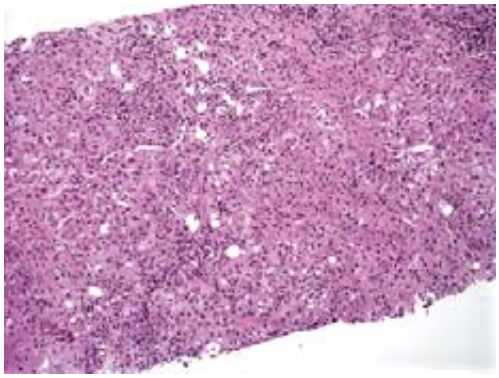

Fig 1. Low power view of liver biopsy with amiodarone toxicity; note patchy steatosis and neutrophilic infiltrate. H&E; original magnification x100.

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was no history of alcohol use. Review of her medications revealed she was on low dose amiodarone which she had been taking for 2 years around the time of AICD placement. On examination, her vital signs were stable. Examiantion revealed asterixis, mild right upper quadrant tenderness and trace ascites. Her initial work up at the outside hospital revealed serum aspartate amino transaminase 377 IU/L, alanine amino transaminase 277 IU/L, alkaline phosphatase 551IU/L, prothrombin time of 12.7 seconds. Serologic studies were negative for chronic viral hepatitis, and there was no clinical or laboratory evidence for autoimmune hepatitis, Wilson's disease, or hemochromatosis. Ultrasound of the liver with Doppler showed homogeneous liver parenchyma and mild ascites. Sections of liver biopsy showed a marked neutrophilic infiltrate with associated degenerating hepatocytes and a remarkable amount of Mallory hyaline with well developed pericellular fibrosis and bridging fibrosis with evidence of early cirrhosis, consistent with amiodarone toxicity (Fig. 2). The patient developed cardiopulmonary failure during her hospital stay and subsequently died.

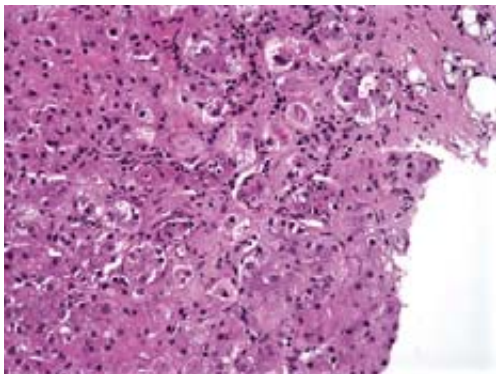

Fig 2. Medium-power view of amiodarone toxicity showing hepatocytes with Mallory hyaline surrounded by neutrophils. H&E; original magnification x200.

Discussion

Amiodarone is lipophilic and thus accumulates in lipid-laden organs such as the liver. This accumulation in the lysosomes of hepatocytes, as well as bile duct epithelium and Kupffer cells leads to a build up of phospholipids which produces a phospholipidosis on the basis of inhibiting phospholipase A1 and A2 [7, 8]. Whether phospholipidosis causes hepatocellular injury is uncertain as liver disease occurs in only 1% to 3% of recipients of amiodarone, while a much larger percentage of patients treated with amiodarone develop phospholipidosis. Therefore, liver injury might occur separate from or in conjunction with phospholipidosis, explaining why cirrhosis rarely occurs in patients treated with amiodarone [1, 2, 6, 9].

Due to its amphophilic nature, amiodarone and its principal metabolite, N-desethylamiodarone, have been detected in serum months after stopping the drug [1, 5]. Because the drug is released slowly from deposits in lysosomes, hepatic abnormalities may persist for one year even after the drug is discontinued [1]. Continued liver damage during treatment with amiodarone may also be secondary to the fact that amiodarone causes hepatic dysfunction initially and further limits the hepatic metabolism, thus further increasing the serum concentration [10]. Consequently, some investigators have speculated that the total cumulative dose might be more important in estimating the risk of irreversible liver injury [11].

It is well known that steatosis and non-alcoholic steatohepatitis (NASH) can be induced by several drugs, including tamoxifen and anti-retroviral agents [12]. These drugs inhibit the mitochondrial β-oxidation of fatty acids and respiration, with resultant decrease in ATP and increased mitochondrial formation of reactive oxygen species. These reactive oxygen species along with lipid peroxidation products may cause mitochondrial dysfunction which can also lead to apoptosis and necrosis, thus activating a cascade leading to fibrosis [13]. Also, many patients receiving amiodarone have underlying diabetes and hyperlipidemia such as our first case and a background of non alcoholic fatty liver disease cannot be ruled out; however, rapid deterioration after instituting amiodarone certainly renders amiodarone usage the most likely causative agent of rapid liver decompensation secondary to cirrhosis. Also, the biopsies were not very suggestive of steatohepatitis and in fact showed Mallory hyaline which is very typical of amiodarone toxicity.

To date, a total 8 cases of amiodarone induced cirrhosis have been reported in the literature [2, 4, 6, 14-19]. As evident from our cases, the range of amiodarone usage for these two cases was between 2 and 3 years. Our inability to accurately assess when the first effects of amiodarone induced hepatotoxicity occurred, makes a pharmacokinetic explanation alone less prudent. A clinical association with initiation of therapy as well as histological features suggestive of amiodarone toxicity strengthens the possibility of a causal relationship. Hence, these cases illustrate the importance of checking baseline liver associated enzymes in patients who are being considered for amiodarone therapy, as well as monitoring them closely during therapy even with low dose amiodarone. Also, strict alcohol cessation must be ensured before the beginning of therapy due to amiodarone effects in causing a pseudo-alcohol like syndrome. It is unclear in the light of present data if amiodarone induced cirrhosis may occur without any abnormalities in liver associated enzymes. It has been suggested that concentrations of amiodarone below a threshold of 1.5 mg/L are associated with a minimal risk of hepatotoxicity, whereas concentrations greater than 2.5 mg/L are associated with a greater than 6% risk of hepatotoxicity. There is significant discordance between changes in amiodarone concentration and the resulting change in ALT. This model suggests that monitoring ALT at baseline, 1, 3, and 6 months, and then semiannually would be an efficient strategy to detect amiodarone-induced hepatotoxicity [20]. Therefore, it would be premature to make suggestions about the necessity of routine imaging or biopsy in these patients.

Conclusion

Patients with amiodarone-induced hepatic dysfunction may have decompensated liver cirrhosis at first presentation. It shall be considered as a differential diagnosis in patients with new onset cirrhosis without any obvious cause. Regular monitoring of liver function tests and low threshold for a liver biopsy to document liver cirrhosis may be considered early in course of disease.

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