

## A Case of Amiodarone-induced Hepatitis and Review of the Literature

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### Abstract

Amiodarone causing side effects on the liver is often discussed in the literature. Amiodarone-induced hepatitis occurs in less than 3% of patients on amiodarone and is easily overlooked. We present a rare case of amiodarone-induced hepatotoxicity causing failure to thrive in an 81 year old man with a history of cryptogenic cirrhosis and further endeavor to discuss a literature review of amiodarone induced hepatotoxicity. Amiodarone-induced hepatitis should be kept in the differential diagnosis of chronic liver disease even in patients with a previous diagnosis of cirrhosis. If the clinical suspicion is high, a liver biopsy is required to make a diagnosis because liver function tests may not be helpful in someone who already has cirrhosis of the liver. Direct hepatotoxicity and idiosyncrasy contribute to liver injury. Chronic liver injury is hypothesized to cause failure to thrive.

**Keywords:** Amiodarone; Hepatitis; Failure to thrive; Antiarrhythmic drug

### Introduction

Since its development in the early 1960s Amiodarone has been a commonly used class III antiarrhythmic drug for the treatment of life threatening cardiac arrhythmias [1]. Amiodarone is an iodine-rich drug that is metabolized in the liver to produce the active metabolite desethylamiodarone. Due to its lipophilic nature, it has strong tissue affinity and a large volume of distribution. It has an unusual spectrum of side effects with a prevalence of 15% in the first year, increasing up to 50% during long term use. However, abnormalities in liver function tests, especially elevated aminotransferase and alkaline phosphatase concentrations, are seen in 4-25% of patients but without consequences [1]. Symptomatic liver disease from oral amiodarone is extremely unusual. Furthermore, amiodarone-induced hepatitis causing failure to thrive is a very unusual presentation of amiodarone which is easily overlooked without a liver biopsy.

### Case Presentation

An 81 year old Caucasian male with a history of hypertension, coronary artery disease, paroxysmal atrial fibrillation, ulcerative colitis and cryptogenic cirrhosis of uncertain duration was admitted with generalized weakness, persistent leukocytosis and failure to thrive. His primary complaint was weight loss of greater than 35 lbs. Over a few months. He was recently discharged when he presented with similar complaints a month prior-at which time he was initially treated with ceftriaxone for suspected spontaneous bacterial peritonitis. However, his ascitic fluid analysis showed 480 white blood cells/cumm with 74% neutrophils. Other tests on his ascitic fluid including cultures yielded normal results. His Aspartate Transaminase during multiple admissions over the previous few months ranged between 120-170 U/L, Alanine Transaminase was between 60-100 U/L, Total Bilirubin was within normal limits and Alkaline Phosphatase was around 170-180 U/L. He underwent extensive testing which included abdominal ultrasound, triple phase abdominal computerized

tomography with liver protocol (Figure 1), esophagogastroduodenoscopy, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (due to elevated CA 19-9 antigen of 271 U/ml and the probability of its association with cholangiocarcinoma) to evaluate for liver and pancreatic pathology.



Figure 1: Liver CT.

A magnetic resonance cholangiopancreatography was not pursued due to the patient's issues with claustrophobia. Several tests were ordered to evaluate the etiology of his liver cirrhosis. His hepatitis panel, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-nuclear antibody and alpha-1-antitrypsin levels were within normal limits. A liver biopsy was not pursued initially as it was unlikely to change management. A peripheral blood smear showed mild leukocytosis (14,700/ml) with borderline monocytosis of 1,650/ml. He was on amiodarone for several years for his paroxysmal atrial fibrillation. This was discontinued due to suspected hepatotoxicity. His laboratory values showed aspartate aminotransferase (AST) was 170 U/L (normal range 5-35), alanine aminotransferase (ALT) was 101 U/L (normal range 0-55) and alkaline phosphatase was 184 U/L (45-115). Total bilirubin, albumin and

PT/INR were within normal limits. An ultrasound guided liver biopsy was obtained which showed severe necro-inflammatory findings and a significant amount of Mallory hyaline (Figure 2) suggestive of chronic active hepatitis and cirrhosis due to amiodarone toxicity.

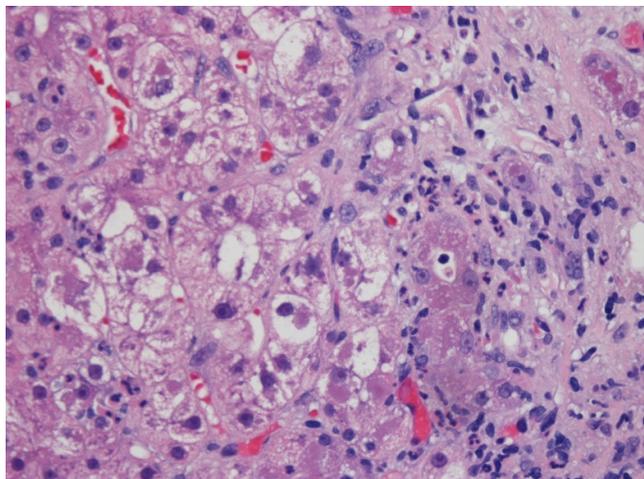


Figure 2: Liver histopathology.

## Discussion

In this era of widespread use of amiodarone, clinicians are well versed with the wide range of its side effects. These include adverse effects on the thyroid, skin, lungs, nerves, and cornea [1]. A transient mild elevation of liver enzymes is found in approximately 15% of the patients. Amiodarone-induced hepatitis and cirrhosis are reported in less than 3% of the patients on amiodarone [1].

Patients who develop amiodarone-induced liver disease are usually asymptomatic in the initial phases. This was demonstrated in a study by Mattar et al. which included 409 patients with mean age of 62 who were expected to be at higher risk for toxicity because of pre-existing liver abnormalities from metabolic syndrome, high prevalence of statin use, and in many cases, heart failure [2]. This study concluded that administration of amiodarone was associated with a low incidence of hepatotoxicity without a relationship to the cumulative dose. Even the presence of metabolic syndrome or right-sided heart failure does not increase the incidence of amiodarone hepatotoxicity [2]. Similarly, no cases of clinical hepatitis, cirrhosis or death related to the therapeutic use of amiodarone were identified in that population during an average period of observation of over 3 years [2,3].

In a 2013 study by Hassain et al. a MEDLINE search from 1970 to 2012 found only 37 reported cases of amiodarone associated with cirrhosis [4]. They also revealed that Aspartate aminotransferase was significantly lower ( $P = 0.03$ ) in patients who survived at 5-months (mean 103.33 IU/L) compared to non-survivors (mean 216.88 IU/L) and demonstrated that amiodarone associated cirrhosis carried a mortality risk of 60% at 5 months once the diagnosis was established [4].

There are indeed a few biopsy proven fatal cases of amiodarone induced liver toxicity reported in literature. These mostly occurred after the use of a high loading dose [5]. Patients with pre-existing heart failure with a lower ejection fraction may also be more prone to the

hepatotoxic effects of amiodarone as reported by Tisdale et al. [6]. Besides chronic liver injury due to prolonged amiodarone use, acute hepatic side effects may occur from an amiodarone intravenous loading dose. This form of acute hepatotoxicity usually improves with discontinuation of medication, although fatalities have been reported [7]. In addition, there are a few case reports of cholestasis that resulted from amiodarone toxicity [8].

Therefore, amiodarone affecting the liver is a very unusual clinical condition, and it is usually recognized if there is a presence of temporal correlation between the abnormal rise in liver function test and amiodarone use. Hence, in any patient who is started on amiodarone, a baseline set of liver function tests and follow up testing every 6 months is recommended. Most of the time, the effect of amiodarone on the liver can easily be recognized in the presence of abnormal liver function tests. But this will be challenging in someone who already has an abnormal liver pathology such as in our case. In those settings, ultrasound guided biopsy is recommended. The histopathologic findings such as Mallory bodies, steatosis, fibrosis and phospholipidosis are commonly associated with amiodarone-induced hepatitis. These changes are similar to alcoholic liver disease. Direct hepatotoxicity and idiosyncrasy of the drug are possible mechanisms contributing to liver injury. Therefore, amiodarone-induced hepatitis should be kept in the differential diagnosis of chronic liver disease even in patients with a previous diagnosis of cirrhosis.

Since amiodarone-induced hepatitis is rare, it can often be overlooked in patients treated for atrial fibrillation even when hepatologists are involved in the care. An injury pattern may present on liver function tests which may not be remarkable. Moreover, it can occur anytime during the course of use of amiodarone and patients may present with very non-specific symptoms such as weakness, fatigue, decreased appetite and weight loss suggestive of failure to thrive. Clinicians should immediately discontinue amiodarone therapy if there is more than a two-fold elevation of transaminases. Considering the possibility of amiodarone as a cause of hepatitis is crucial in patients on chronic amiodarone therapy to prevent permanent hepatic damage.

There is still an ongoing debate in the medical community as to why some patients have a higher propensity to develop cirrhosis or hepatic damage as a side effect of amiodarone. The risk factors predisposing to the development of amiodarone-induced cirrhosis and hepatitis are not yet entirely clear. The existence of differing sensitivity to amiodarone toxicity in different populations has also been suggested. The relation of hepatotoxicity to cumulative dose and duration of therapy is debated [9]. Evidence pertaining to both mild and severe amiodarone related hepatotoxicity indicates that cumulative dose may correlate with overall toxicity and, therefore, maintenance doses should be kept as low as possible. One meta-analysis showed that a mean amiodarone dose of 152 mg to 330 mg per day for duration of at least 12 months resulted in odds similar to those of placebo for hepatic and gastrointestinal adverse effects but significantly higher odds than those of placebo ( $p < 0.05$ ) for experiencing thyroid, neurologic, skin, ocular and bradycardic adverse effects [10]. Most patients who developed amiodarone-induced cirrhosis usually used amiodarone PO 200 mg or more per day for more than 1-2 years. A cumulative dose of 380 g is suggested to have an association with hepatotoxicity leading to cirrhosis [11]. Why some patients with a cumulative dose of 200 g develop cirrhosis and others do not until the cumulative dose crosses above 1000 g is unclear, but it does suggest that it may be a steady state concentration rather than a cumulative dose that may be important in

predicting risk of cirrhosis. Other prospective studies have shown that amiodarone related hepatic toxicity correlates to steady state serum levels of amiodarone rather than daily or cumulative doses [12]. For example, if a daily dosage of amiodarone during long-term therapy is reduced, despite the fact that the lifetime cumulative dose continues to increase, the steady state serum concentration will still be reduced, thus decreasing the risk of hepatotoxicity. Researchers have suggested that an amiodarone level less than 1.5 mg/L has a minimal risk of hepatotoxicity, whereas a level above 2.5 mg/L may have a risk of up to 6% for hepatotoxicity [13]. Because of its 55-day half-life, it takes 6-8 months for amiodarone to reach steady state. This is the time frame upon which most studies correlate cumulative dose with toxicity [3]. In our case, the patient was taking amiodarone 100 mg PO BID for several years. We did not check the amiodarone level in the blood but likely due to the presence of other chronic medical problems he developed hepatitis. Therefore, careful monitoring of amiodarone is recommended in patients with multiple comorbidities because it produces a range of potentially severe adverse effects. Potential hepatotoxicity related to amiodarone therapy is often a concern when deciding whether to initiate or continue treatment with this medication. While mostly associated with long-term oral administration of the drug, toxicity has also been reported early during intravenous administration and even after months upon discontinuation of therapy. In the majority of patients, it is discovered incidentally during routine testing of liver biochemistry and rarely do the hepatic effects develop into symptomatic liver injury or failure. Despite the widespread use of amiodarone, prospective clinical studies have been sparse and there has been little consensus among experts in the field regarding optimum monitoring for adverse effects in patients receiving this drug [9]. Therefore, patients should be followed with monitoring of liver function test results every 3-6 months [9].

Serum enzyme elevations are reported to occur in 15% to 50% of patients on long term therapy. However, with lower doses (200 mg to 300 mg daily), ALT elevations are less common [4]. Also, pre-existing liver dysfunction was not predictive of transaminitis in a population of 720 Chinese patients. Kum et al. demonstrated that not only did a large proportion of their patient population of patients using amiodarone had ALT abnormalities at baseline (14.3%), but also that the incidence of significant liver dysfunction was not statistically different (4.4 vs. 3.7%) in patients with or without elevated baseline ALT [14].

In conclusion, amiodarone induced liver injury is usually limited to asymptomatic transaminitis that resolves either spontaneously or after dose reduction. But amiodarone does cause hepatitis similar to alcohol at any time in the course during use which may manifest with very

nonspecific symptoms. Despite the fact that there is a lot of discussion about the hepatotoxic effects of amiodarone, good quality evidence of high rates of toxicity such as hepatitis does not exist in the literature, especially on amiodarone at moderate doses. No prospective follow-up or retrospective case studies have identified a high rate of clinical hepatotoxicity so far.

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