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Amiodarone-induced Hepatitis and Polyneuropathy

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Amiodarone chlorhydrate is a diiodated benzofuran derivative, and it is used to treat cardiac rhythm abnormalities. Hepatotoxicity is a relatively uncommon side effect of amiodarone, and symptomatic hepatic dysfunction occurs in fewer than 1% of the patients taking amiodarone. Cirrhosis is a rare complication that's been confirmed in 12 cases. Peripheral neuropathy occurs in 10% of patients taking aminodarone. We report here on an unusual case of amiodarone-induced hepatotoxicity and peripheral neurotoxicity. A 75 year old man with normal liver function was given amiodarone for treating his atrial fibrillation and heart failure. He developed nausea, vomiting, muscle weakness and wasting after 17.8 months therapy with amiodarone (400 mg orally once per day). Liver biopsy showed the presence of foam cells in the hepatic sinusoids and Mallory bodies in the periportal hepatocytes on light microscopy. Sural nerve biopsy showed demyelination, and nerve conduction studies showed mixed sensorimotor polyneuropathy. These observations show the necessity of monitoring the hepatic function and conducting neurologic examination of the patients treated with amiodarone.

Key Words : Amiodarone, Hepatitis, Polyneuropathy

INTRODUCTION

Amiodarone is an iodine-rich drug that is a highly effective and widely used as an antiarrhythmic agent for the treatment of symptomatic supraventricular and ventricular tachyarrhythmias. Amiodarone is associated with many adverse effects that involve different organs. Although these side effects are generally mild, 10～15% of patients require withdrawal of the drug as a result of toxicity. The most prominent adverse effects during long-term therapy include thyroid dysfunction, corneal microdeposits and pulmonary and hepatic toxicity[1]. Transient rises in hepatic enzyme activity have been reported in 40% of the patient who received the antiarrhythmic agent amiodarone[2]. Asymptomatic elevation of serum aminotransferases occurs in 25% of those patients who are treated with aniodarone. However, the prevalence of severe liver injury has been estimated at only 1% to 3%[3]. Micronodular cirrhosis that was clearly due to amiodarone therapy has been confirmed in 12 cases[4]. Muscle weakness and peripheral neuropathy have also been reported in 10% of the patients who were administered the anti-arrhythmic agent amiodarone[5, 6]. We describe here a case of amiodarone-induced hepatitis and neuropathy after treatment with 400 mg of oral amiodarone for 17.8 months.

CASE REPORT

A 75 year old man was hospitalized in December 2005 due to nausea, vomiting and difficulty in walking and raising his legs to walk up steps for the previous three months. Since July 2004, the patient had been given amiodarone 400 mg daily for treating his atrial fibrillation and heart failure. His heart rhythm was

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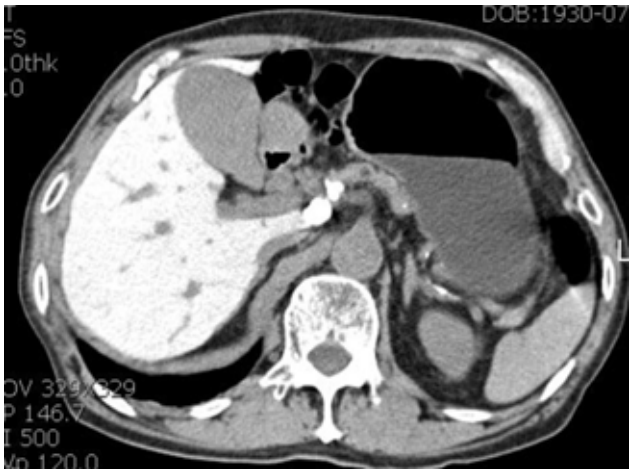

Figure 1. Pre-enhanced computed tomogram of the abdomen showing diffuse high attenuation of the liver parenchyma.

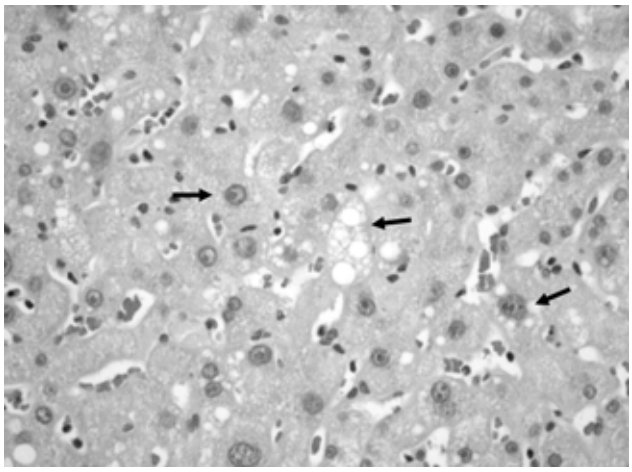

Figure 2. Liver biopsy showing clusters of foam cells in the hepatic sinusoidal spaces and micro-& and macrovesicular fatty change (H&E, ×200).

converted to sinus rhythm after amiodarone therapy.

He had a history of pulmonary tuberculosis, which was treated with anti-tuberculosis drugs 30 years prior to this hospitalization. He had drank 40 g of alcohol per day for 20 years before his abstinence from drinking 4 months ago. His other medications at admission were carvediol 12.5 mg twice per day, diltiazem 30 mg twice per day and triflusal 300 mg once per day. He denied the use of other hepatotoxic drugs or toxins. His liver function before amiodarone therapy was normal. He denied any current cardiovascular or pulmonary symptoms. The vital signs were normal. His body weight and body mass index were 50 kg and 17.7, respectively. Neurologic examination showed striking bilateral weakness of the hip and knee flexors and extensors. The weakness became more diffuse, affecting the proximal muscles more than the distal muscles. There weren't a fluid ware, shifting dullness and pretibial pitting edema. The other physical examination was also nonspecitic. The laboratory findings on the admission were as follows: serum aspartate aminotransferase 123 IU/L; serum alanine aminotransferase 146 IU/L; serum albumin 2.5 g/dL; serum bilirubin 0.8 mg/dL; alkaline phosphatase 99 IU/L;platelets 212,000 cells/*u*L; blood hemoglobin 13.1 g/dL; negative results of tests for hepatitis B surface antigen, hepatitis A antibody, hepatitis C antibody and the VDRL test. The serum fasting transferrin saturation level was normal. The serum antinuclear antibody was positive, but other autoantibodies, including anti-dsDNA, anti-Sm and anti-Ro, anti-La antibody were negative. Also, the anti-smooth muscle and anti-mitochondrial antibodies were negative. The thyroid function test and urine analysis were within the normal limits. A pre-enhanced computed tomogram of the abdomen showed diffuse high attenuation of the liver parenchyma (Figure 1). Liver biopsy showed microvesicular steatosis, foam cells in the hepatic

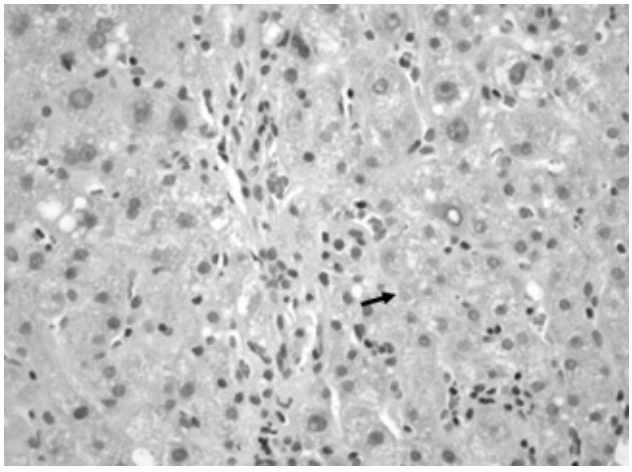

Figure 3. Periportal liver cells contain Mallory bodies (H&E, ×200).

sinusoids and mallory bodies in the periportal hepatocytes, and also features of chronic hepatitis (mild lobular activity, grading score 2; minimal porto-peripheral activity, grading score 1; portal fibrosis, staging score 1) on the light microscopy (Figure 2-4). With electron microscopy, the hepatocytes showed pleomorphic mitochondria that had crystalloid inclusions and focal concentric membranous arrays, which suggested membrane-bound lysosomal structures. Both findings strongly suggested amiodarone-induced hepatotoxicity.

Nerve conduction studies and electromyography were performed after admission. They suggested sensorimotor polyneuropathy with both axonal degeneration and demyelination (Table 1, 2). The neurophysiologic investigations showed slowing of the sensory and motor conduction velocities, delay of the distal latencies and F-wave latencies of the motor nerves, and delay of the H-reflex latency of the tibial nerve. The

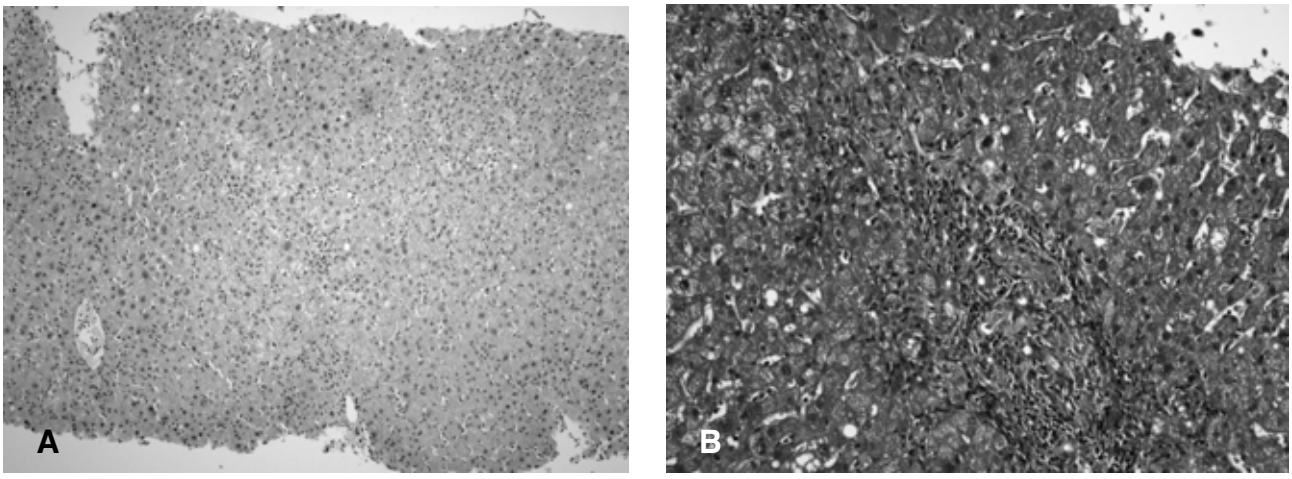

Figure 4. Liver biopsy showed mild lobular activity (A, H&E, ×100), minimal periportal activity and fibrous portal expansion (B, Masson's Trichrome stain, ×200).

Table 1. Motor nerve conduction studies

Motor nerve				Normal values
Peroneal nerve	MCV	m/s	32	41.65
	DL	ms	5.1	4.78
	F. Lat	ms	63.6	50.03
	Amp	mV	1.0	5.0
Post. tibial nerve	MCV	m/s	41	40.63
	DL	ms	5.4	5.11
	F. Lat	ms	59.7	52.02
	Amp	mV	3.0	5.0
Ulnar nerve	MCV	m/s	42	50.61
	DL	ms	3.5	2.51
	F. Lat	ms	33.7	29.04
	Amp	mV	7.4	5.0
Median nerve	MCV	m/s	49	49.96
	DL	ms	3.8	3.60
	F. Lat	Ms	31.4	28.85
	Amp	mV	12.4	5.0

MCV, motor conduction velocity; DL, distal latency; F. Lat, F-wave latency; Amp, potential amplitude

histologic findings from the sural nerve showed focal demyelination (Figure 5). Amiodarone was withdrawan and the patients experienced temporary clinical improvement. The liver enzyme activity on day 3 after amiodarone withdrawal was as follows: serum aspartate aminotransferase 31 IU/L; serum alanine aminotransferase 27 IU/L. The interruption of amiodarone therapy improved the neuropathy. The patient fully recovered from the muscle weakness and nausea at 1 month after the cessation of amiodarone.

DISCUSSION

Amiodarone is lipophilic, and so it accumulates in lipid-laden organs such as the liver. Amiodarone and its major metabolite, N-desethylamiodarone, accumulate in the lysosomes of the hepatocytes, Kupffer cells and bile duct epithelium. The cationic amphophilic amiodarone molecule binds to phospholipids in the lysosomes and forms a nondigestable complex[7, 8]. This causes accumulation of phospholipids in lysosomes, resulting in secondary phospholipidosis. The presence of foam cells in the hepatic sinusoids on light microscopy and the membrane-bound lysosomal structures (lamellated inclusions) or the crystalloid inclusions on electron microscopy suggest phospholipidosis[3, 7, 9]. These finding, such as foam cells in the hepatic sinusoids and crystalloid inclusions were also seen on our studies. It is uncertain whether hepatocellular injury is due to phospholipidosis[6] or the metabolic effects of amiodarone and its

Table 2. Sensory nerve conduction studies and the H-reflex study

				Normal values
Medianl nerve	SCV	m/s	37	49.39
	S.pot.ampl	uV	10	10
Ulnar nerve	SCV	m/s	36	47.46
	S.pot.ampl	uV	9	8
Sural nerve	SCV	m/s		34.68
	S.pot.ampl	uV	No potential	6
H-reflex on tibial nerve	Latency	ms	40.8	30.5

SCV, sensory conduction velocity; DL, distal latency; F. Lat, F-wave latency; S.pot.ampl, sensory potential amplitude

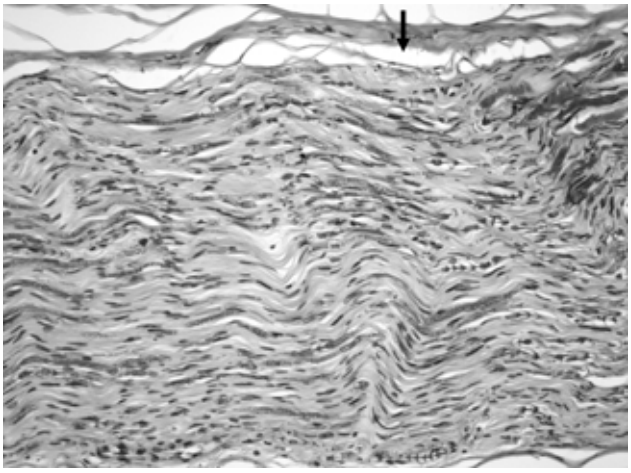

Figure 5. The sural nerve biopsy shown in longitudinal section with light microscopy consists of a single fascicle that is not invested by the perineurium (H&E, ×200).

metabolites[3, 9]. Yet the accumulation of lamellated inclusion bodies suggests a drug-induced disturbance of both lipid metabolism and lysosomal function[6]. Rheumatic diseases were excluded because there were no abnormal clinical findings or autoimmune antibodies except for serum antinuclear antibody. Peripheral neuropathy associated with amiodarone was first reported by Kaeser in 1974[10]. Three types of neuropathy have been reported, that is, axonal by Meier et al[11], demyelinating by Kaeser et al[12], and mixed by Dudognon et al[13]. Pellissier et al described that the neuropathy is of a sensorimotor type[14]. In that study, the daily dose of amiodarone until the onset of neuropathy was 50～1,800 mg, and the treatment duration was 1～168 months[14]; there was no correlation between neuropathy and the daily dose, the total dose or treatment duration. These discrepancies of the dose and treatment duration may suggest interindividual variability of amiodarone metabolism[14]. In our current case, leg weakness occurred 14 months after starting medication with a daily dose of 400 mg amiodarone, and walking difficulty happened after 16 months. Examination of the sural nerves showed characteristic amiodarone-induced lamellated inclusions in many cell types. These inclusions are known to be lysosomal in origin, and they are a characteristic finding of amiodarone-induced neuropathy[15]. The peripheral neuropathy is generally resolved within 3 days to 3 months of discontinuing amiodarone[16]. In our case, the patient's muscle weakness improved after 2 weeks and ambulation was possible at 1 month after the cessation of taking amiodarone. Even though we did not perform an electron microscopic exam on the sural nerve, we consider the neurologic findings of our patient to be amiodarone-induced neuropathy for many reasons. Not only because of the test results such as the mixed sensorimotor polyneuropathy findings on nerve conduction velocity studies and electromyography, and the demyelination findings on the sural nerve biopsy, but also the clinical findings such as muscle weakness and the improvement after cessation of amiodarone are enough to make the correct diagnosis. That the patients had no other definite cause for neuropathy also supports our diagnosis. Careful questioning of past drug exposure is essential for any patient with altered biochemical liver tests and neurologic symptoms. We suggest that amiodarone should be withdrawn if a patient shows neurologic symptoms or if the liver function test results are abnormal. By doing so, it is possible to avoid unnecessary, costly diagnostic evaluation and severe toxicity.

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