

**[ CASE REPORT ]**

## Changes in Hepatic Density Due to Oral Amiodarone-induced Liver injury Shown by Computed Tomography

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### Abstract:

Amiodarone is an antiarrhythmic drug that is widely used for atrial fibrillation and other refractory arrhythmias. Although beneficial, its long-term administration is associated with adverse effects on various organs. One patient presented with amiodarone-induced liver injury, which led to liver failure. Computed tomography revealed a gradual increase in hepatic density over a long period following the initiation of amiodarone. Despite the discontinuation of the drug, the patient developed hepatic encephalopathy and subsequently died. This outcome highlights the drug's extended half-life, which caused persistent end-organ damage even after its withdrawal. Drug titration to the lowest effective dose and careful monitoring of annual liver function tests are important.

**Key words:** amiodarone, liver injury, hepatic density on computed tomography

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### Introduction

Amiodarone is an effective antiarrhythmic agent classified as Vaughan-Williams class III and is frequently used during the perioperative period (1). Nevertheless, long-term oral use of this agent has been associated with adverse effects such as photosensitivity, thyroid dysfunction, and pulmonary and hepatic toxicity (2). The molecular structure of amiodarone includes iodine; thus, with its accumulation in the liver, there is an increase in hepatic density, which can be seen by computed tomography (CT). Hepatic density noted in CT findings is correlated with the blood level of desethyl-amiodarone, a metabolite of amiodarone (3).

We herein report a case of liver injury caused by the long-term administration of oral amiodarone. The findings included changes in hepatic density shown by CT prior to the beginning of oral administration until the end stage of liver failure.

### Case Report

A 74-year-old woman underwent mitral valvuloplasty for severe mitral regurgitation with New York Heart Association functional classification (NYHA class) II. Atrial fibrillation developed during the perioperative period, and oral administration of amiodarone (200 mg) was started, with the prescription continued by a local doctor after discharge. Six years after undergoing mitral valvuloplasty, the patient was referred to our department because of elevated liver enzyme levels.

The patient was prescribed amiodarone (200 mg), atorvastatin (10 mg), vonoprazan (20 mg), diltiazem (90 mg), and warfarin (1 mg) and had no drinking or smoking habits. Anthropometric measurements revealed that her body weight was 48.9 kg, her height was 155.4 cm, and her body mass index was 20.2 kg/m<sup>2</sup>. A physical examination revealed no findings indicative of icterus or asterixis, although her abdomen was distended. Other results indicated a blood pressure

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**Table 1. Laboratory Data.**

|                   |                                         |                             |                |
|-------------------|-----------------------------------------|-----------------------------|----------------|
| WBC               | 9,500 / $\mu$ L                         | Sodium                      | 143 mEq/L      |
| Neut              | 82 %                                    | Potassium                   | 3.5 mEq/L      |
| Lympho            | 12.5 %                                  | Chloride                    | 106 mEq/L      |
| Mono              | 5.4 %                                   | Calcium                     | 9.1 mg/dL      |
| RBC               | 3.66 $\times$ 10 <sup>6</sup> / $\mu$ L | HbA1c                       | 4.7 %          |
| Hemoglobin        | 11.3 g/dL                               | CRP                         | 0.58 mg/dL     |
| Hematocrit        | 34.9 %                                  | Ferritin                    | 130 ng/mL      |
| Platelet          | 12.7 $\times$ 10 <sup>4</sup> / $\mu$ L | FT3                         | 1.6 pg/mL      |
| PT                | 27.5 %                                  | FT4                         | 1.8 pg/mL      |
| PT-INR            | 2.56                                    | TSH                         | 1.8 $\mu$ U/mL |
| APTT              | 43.7 s                                  | HCV antibody                | (-)            |
| D-dimer           | 2.1 $\mu$ g/mL                          | HBs antigen                 | (-)            |
| Total protein     | 6 g/dL                                  | HBc antibody                | 4.1            |
| Albumin           | 3.1 g/dL                                | HBV DNA                     | (-)            |
| T-bilirubin       | 0.6 mg/dL                               | Immunoglobulin G            | 1,269 mg/dL    |
| AST               | 120 U/L                                 | Immunoglobulin A            | 285 mg/dL      |
| ALT               | 114 U/L                                 | Immunoglobulin M            | 183 mg/dL      |
| LDH               | 383 U/L                                 | Immunoglobulin E            | 50 IU/mL       |
| Amylase           | 48 U/L                                  | Antinuclear antibody        | (-)            |
| Triglyceride      | 84 mg/dL                                | Anti-mitochondrial antibody | (-)            |
| Total cholesterol | 196 mg/dL                               | KL-6                        | 477 U/mL       |
| BUN               | 24.9 mg/dL                              | Amiodarone                  | 1,538 ng/mL    |
| Creatinine        | 0.96 mg/dL                              | Desethyl-amiodarone         | 1,540 ng/mL    |

WBC: white blood cells, RBC: red blood cells, PT: prothrombin time, PT-INR: PT-international normalized ratio, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, HbA1c: hemoglobin A1c, CRP: C-reactive protein, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulating hormone, HCV: hepatitis C virus, HBs: hepatitis B surface, HBc: hepatitis B core, HBV: hepatitis B virus

of 123/59 mmHg, oxygen saturation of 96% on room air, heart rate of 84 beats/min, and body temperature of 36.4°C.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 120 U/L and 114 U/L, respectively, while triglyceride, total cholesterol, and hemoglobin A1c levels were within the normal ranges. Ferritin levels were not elevated at 130 ng/mL, and there was no evidence of abnormal thyroid function. Hepatitis virus examination results were positive only for the antibody to Hepatitis B core antigen, while Hepatitis B surface, Hepatitis B Virus-DNA, and anti-Hepatitis C Virus antibody were negative, indicating a previous hepatitis B virus infection. No autoantibody abnormalities were observed. Her KL-6 level was within the normal range at 477 U/mL. Her blood concentration of amiodarone, with an effective range of 500-1000 ng/mL, was increased to 1538 ng/mL, while that of desethyl-amiodarone, a metabolite of amiodarone, was also elevated at 1540 ng/mL (Table 1).

Abdominal ultrasonography of the liver showed an irregular surface and rough parenchymal echogenicity, while ascites and splenomegaly (suggestive of liver cirrhosis) were also noted. Hepatorenal echo contrast was negative (Fig. 1). Non-enhanced CT revealed diffuse ground-glass opacities in both lung fields (Fig. 2A), whereas liver atrophy was predominant in the right lobe, indicating liver cirrhosis. Increased hepatic density and ascites accumulation were ob-

served (Fig. 2B).

A review of previous laboratory data showed a gradual increase in liver enzymes (AST and ALT) during the 6 years since the start of amiodarone treatment. CT findings showed that the hepatic density prior to the initiation of oral amiodarone was normal at 60 Hounsfield units (HU), then gradually increased to 67 HU after 1 year of amiodarone treatment, 79 HU after 4 years, and 102 HU after 6 years (Fig. 3).

The patient's liver enzyme levels and hepatic density on CT increased after the initiation of amiodarone, and other possible causes, such as viral hepatitis, autoimmune disease, and metabolic liver injury, were ruled out. Our diagnosis was amiodarone-induced liver injury, and the discontinuation of amiodarone temporarily improved her serum liver enzyme levels. However, despite medical management, the patient subsequently developed hepatic encephalopathy and died of liver failure 10 weeks after being referred to our department (Fig. 4).

## Discussion

The multisystemic side effects of amiodarone have become more apparent with the growing trend in its use. Pulmonary toxicity is one of the most common adverse effects of long-term amiodarone therapy and is responsible for most

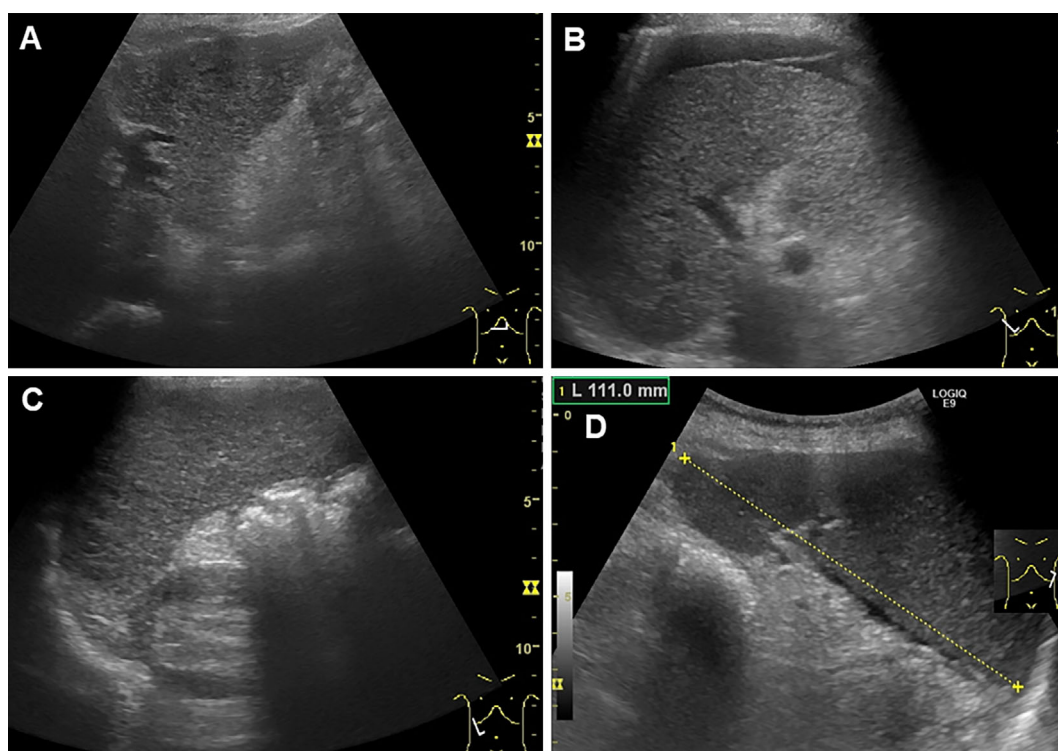


**Figure 1.** Liver abdominal ultrasonography findings. (A) An irregular liver surface and rough parenchymal echogenicity suggest liver cirrhosis. (B) Ascites around the liver. (C) Hepato-renal echo contrast was negative. (D) Splenomegaly (long diameter, 111 mm) was noted.

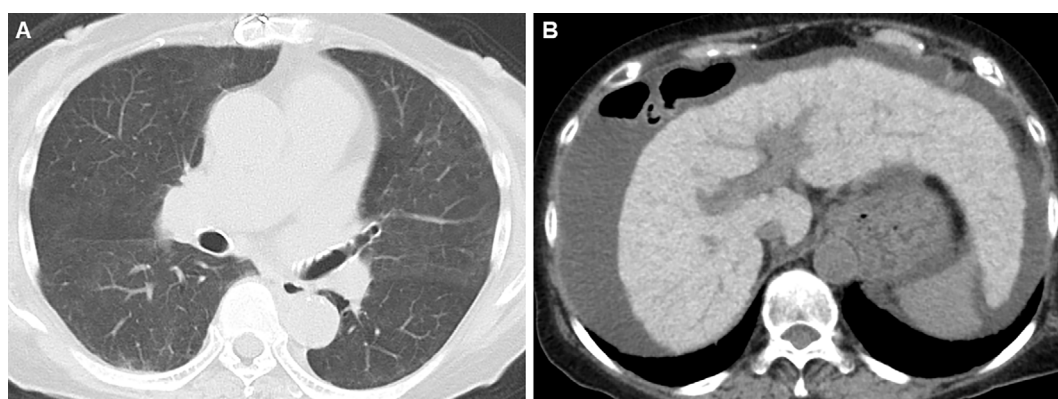


**Figure 2.** Non-enhanced computed tomography images at the time of referral to our department. (A) Diffuse ground glass opacities in both lung fields. (B) Liver atrophy was predominant in the right lobe, indicating cirrhosis. Furthermore, increased hepatic density and the accumulation of ascites were observed.

of the rare deaths associated with amiodarone (4). Another study noted that the prevalence of pulmonary toxicity can reach up to 20% (5). Amiodarone-induced liver injury was first reported by Plomteux et al. in 1969 (6). Transient elevation of liver enzymes occurs in approximately 25% of patients taking amiodarone (7). More severe complications, such as hepatitis and cirrhosis, are less common and are estimated to affect less than 3% of patients treated with amiodarone (5).

Although the precise mechanism of amiodarone-related hepatic toxicity has not been elucidated, there are two possi-

ble explanations. First, amiodarone accumulates in the lysosomes of hepatic macrophages and interacts with phospholipids to form drug-lipid complexes, which injure the lipid bilayer of hepatocytes (7, 8). Second, amiodarone inhibits mitochondrial  $\beta$ -oxidation of hepatocyte cells and activation of oxygen radicals while also causing apoptosis of hepatocytes, leading to non-alcoholic steatohepatitis (NASH) (9). The present patient was assumed to have developed burned-out NASH because the abdominal ultrasonography findings were negative for hepatorenal echo contrast.

Amiodarone and its metabolite desethyl-amiodarone pri-

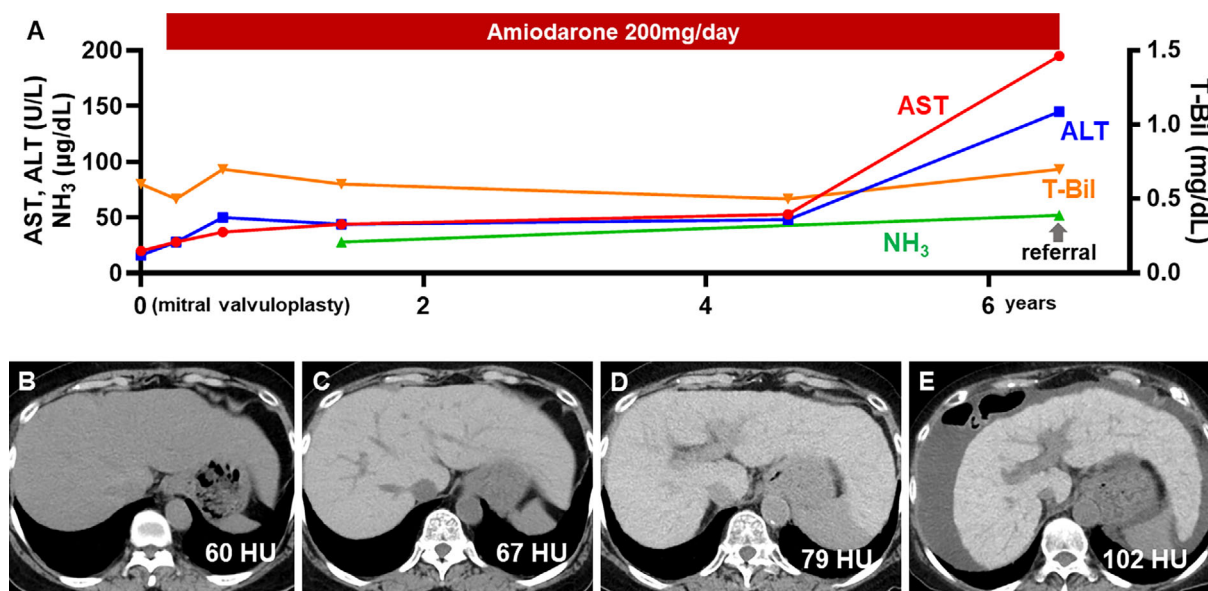


**Figure 3.** Liver enzyme levels and hepatic density trends shown by non-enhanced computed tomography (CT). (A) Trends in liver enzyme [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin (T-Bil), and ammonia ( $\text{NH}_3$ ) levels. AST and ALT levels gradually increased during the 6-year period after the initiation of amiodarone. (B) Abdominal CT findings prior to amiodarone administration showed a normal density of 60 Hounsfield units (HU). (C) Abdominal CT findings 1 year after the initiation of amiodarone showed a slight increase in density to 67 HU. (D) Abdominal CT findings 4 years after the initiation of amiodarone showed a continued increase in density to 79 HU. (E) Abdominal CT findings 6 years after the initiation of amiodarone administration showed a further increase in density to 102 HU.

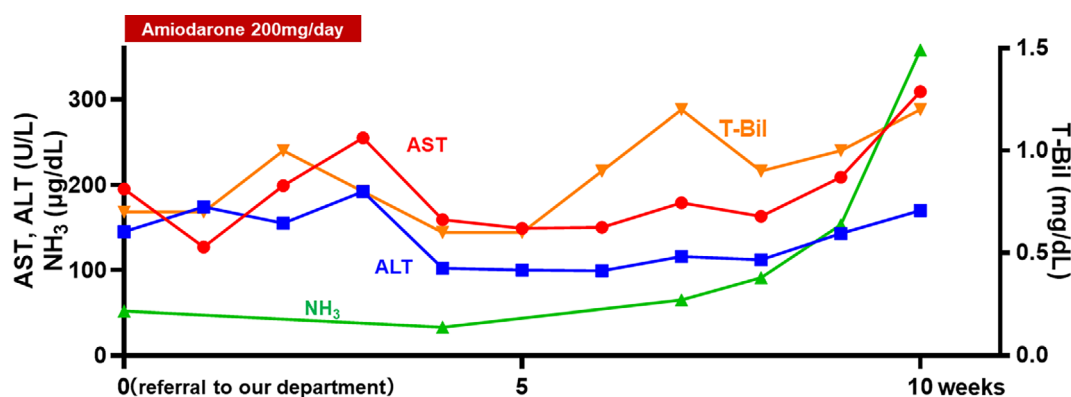


**Figure 4.** Trends of liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin (T-Bil), and ammonia ( $\text{NH}_3$ ) levels following referral. Initially, the discontinuation of amiodarone resulted in temporary improvements in serum liver enzyme levels. However, despite medical management, the patient subsequently developed hepatic encephalopathy and died 10 weeks after referral to our department.

marily accumulate in the liver rather than in the skeletal muscle or spleen (10). As amiodarone is rich in iodine, containing 37% iodine by weight, and iodine exhibits a high density on CT scans, the hepatic density on CT is likely to be elevated in cases of amiodarone-induced liver injury (11).

Conditions associated with increased hepatic density shown by CT include certain metal deposition diseases such as hemochromatosis, hemosiderosis, Wilson's disease, and glycogen storage diseases (12). Hemochromatosis and he-

mosiderosis were considered unlikely in the present case because the serum ferritin level and splenic density shown by CT were both normal, while Wilson's disease was excluded because of a negative family history and no known neuropsychiatric symptoms. Glycogen storage diseases can also be ruled out based on the clinical history.

Ten clinical reports regarding amiodarone-induced liver injury with increased hepatic density shown by CT prior to the present study have been presented (Ta-

**Table 2. Summary of the Ten Reported Patients of Amiodarone-induced Liver Injury with Increased Hepatic Density on CT and Present Case.**

| Case | Age | Sex | Cumulative amiodarone dose (g) | Duration of amiodarone administration (month) | Blood concentration of amiodarone (ng/mL) | Blood concentration of desethylamiodarone (ng/mL) | AST (U/L) | ALT (U/L) | CT density (HU) | Prognosis | Year | References   |
|------|-----|-----|--------------------------------|-----------------------------------------------|-------------------------------------------|---------------------------------------------------|-----------|-----------|-----------------|-----------|------|--------------|
| 1    | 85  | M   | 511                            | 84                                            | N/A                                       | N/A                                               | 81        | 35        | 111.8           | improve   | 2005 | (13)         |
| 2    | 75  | M   | 213.6                          | 17.8                                          | N/A                                       | N/A                                               | 123       | 146       | high (HU N/A)   | improve   | 2007 | (14)         |
| 3    | 60  | M   | 216                            | 18                                            | 1,554                                     | 1,456                                             | N/A       | N/A       | 113             | improve   | 2009 | (10)         |
| 4    | 75  | F   | 312                            | 26                                            | 900                                       | N/A                                               | 44.1      | 50        | 100             | improve   | 2014 | (15)         |
| 5    | 66  | F   | 876                            | 72                                            | N/A                                       | N/A                                               | 220       | 189       | 90              | improve   | 2017 | (3)          |
| 6    | 62  | M   | 771.75                         | 156                                           | 1,800                                     | 1,100                                             | 161       | 106       | 96              | dead      | 2018 | (16)         |
| 7    | 74  | M   | 219                            | 36                                            | 1,400                                     | N/A                                               | 189       | 150       | 120             | improve   | 2018 | (16)         |
| 8    | 66  | M   | 730                            | 120                                           | N/A                                       | N/A                                               | 101       | 127       | 118             | improve   | 2020 | (17)         |
| 9    | 77  | F   | 146                            | 24                                            | N/A                                       | N/A                                               | 160       | 161       | 148             | dead      | 2023 | (18)         |
| 10   | 50s | M   | N/A                            | 36                                            | 649                                       | 1,199                                             | 861       | 1,601     | 100             | improve   | 2023 | (19)         |
| 11   | 74  | F   | 438                            | 72                                            | 1,538                                     | 1,540                                             | 120       | 114       | 102             | dead      | 2024 | present case |

AST: aspartate aminotransferase, ALT: alanine aminotransferase, CT: computed tomography, HU: Hounsfield units, N/A: not available

ble 2) (3, 10, 13-19). Due to the small number of cases, a statistical analysis could not be performed. Nevertheless, a review of these findings indicated little or no relationship between the blood amiodarone concentration and CT density or the prognosis. A systematic search of 30 reported cases of amiodarone-induced liver cirrhosis diagnosed between 1970 and 2012, although without CT density findings, showed that AST was significantly lower in survivors at 5 months after the diagnosis (20).

For patients undergoing chronic amiodarone therapy, annual examinations of serum transaminase levels (AST and ALT) are recommended to monitor side effects (5). Our patient was prescribed amiodarone continuously by a local clinic, and blood tests were performed only once every two years. Previous tests revealed a gradual increase in transaminase levels, which was initially attributed to liver congestion secondary to a poor cardiac function. In addition to amiodarone, the patient was taking multiple other medications. Given this polypharmacy and rising liver enzyme levels, a comprehensive evaluation of drug-induced liver injury should have been conducted earlier.

To the best of our knowledge, this is the first documented case of changes in hepatic density shown by CT, tracked from the period before amiodarone administration to end-stage liver failure. While the discontinuation of amiodarone is recommended for patients presenting with hepatic failure, the long half-life of 35-110 days and the large distribution volume often lead to persistent end-organ damage, even after its withdrawal (20). Therefore, it is important to titrate the drug to its lowest effective dose and to carefully monitor the results of routine liver function tests for possible multi-systemic adverse effects in patients receiving amiodarone therapy.

**The authors state that they have no Conflict of Interest (COI).**

## References

- Epstein AE, Olshansky B, Naccarelli GV, Kennedy JI Jr, Murphy EJ, Goldschlager N. Practical management guide for clinicians who treat patients with amiodarone. *Am J Med* **129**: 468-475, 2016.
- Essrani R, Mehershahi S, Essrani RK, et al. Amiodarone-induced acute liver injury. *Case Rep Gastroenterol* **14**: 87-90, 2020.
- Ozkurt H, Asmakutlu O, Uysal E, Basak M. Hepatic hyperattenuation on CT caused by using amiodarone: report of a case. *J Radiol Radiat Ther* **5**: 1074-1076, 2017.
- Budin CE, Cocuz IG, Sabău AH, et al. Pulmonary fibrosis related to amiodarone-is it a standard pathophysiological pattern? a case-based literature review. *Diagnostics* **12**: 3217, 2022.
- Goldschlager N, Epstein AE, Naccarelli G, Olshansky B, Singh B; Practice guidelines subcommittee, North American Society of Pacing and Electrophysiology. Practical guidelines for clinicians who treat patients with amiodarone. *Arch Intern Med* **160**: 1741-1748, 2000.
- Plomteux G, Heusghem C, Ernould H, Vandeghen N. Long-term hepatic tolerance of amiodarone in the clinic. *Eur J Pharmacol* **8**: 369-376, 1969.
- Lewis JH, Ranard RC, Caruso A, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology* **9**: 679-685, 1989.
- Jafari-Fesharaki M, Scheinman MM. Adverse effects of amiodarone. *Pacing Clin Electrophysiol* **21**: 108-120, 1998.
- Wanderer F, Frangež Ž, Liebig S, et al. Autophagy alleviates amiodarone-induced hepatotoxicity. *Arch Toxicol* **94**: 3527-3539, 2020.
- Kojima S, Kojima S, Ueno H, Takeya M, Ogawa H. Increased density of the liver and amiodarone-associated phospholipidosis. *Cardiol Res Pract* 598940, 2009.
- Sohn SY, Inoue K, Rhee CM, Leung AM. Risks of iodine excess. *Endocr Rev*. Forthcoming.
- Boll DT, Merkle EM. Diffuse liver disease: strategies for hepatic CT and MR imaging. *Radiographics* **29**: 1591-1614, 2009.
- Oikawa H, Maesawa C, Sato R, et al. Liver cirrhosis induced by long-term administration of a daily low dose of amiodarone: a case report. *World J Gastroenterol* **11**: 5394-5397, 2005.
- Kang HM, Kang YS, Kim SH, et al. Amiodarone-induced hepatitis and polyneuropathy. *Korean J Intern Med* **22**: 225-229, 2007.

15. Kim BB, Kim DM, Choi DH, et al. Amiodarone toxicity showing high liver density on CT scan with normal liver function and plasma amiodarone levels in a long-term amiodarone user. *Int J Cardiol* **172**: 494-495, 2014.
16. Tsuda T, Tada H, Tanaka Y, et al. Amiodarone-induced reversible and irreversible hepatotoxicity: two case reports. *J Med Case Rep* **12**: 95, 2018.
17. Lv HJ, Zhao HW. Amiodarone-induced hepatotoxicity - quantitative measurement of iodine density in the liver using dual-energy computed tomography: three case reports. *World J Clin Cases* **8**: 4958-4965, 2020.
18. Tun MM, Pandey S, Adhikari S, et al. Amiodarone-induced liver attenuation on CT scan: alarming signal for toxicity and prompt discontinuation. *Cureus* **15**: e39844, 2023.
19. Nagata T, Takata K, Shakado S, Hirai F. Amiodarone-induced hepatotoxicity. *BMJ Case Rep* **16**: e256679, 2023.
20. Hussain N, Bhattacharyya A, Prueksaritanond S. Amiodarone-induced cirrhosis of liver: what predicts mortality? *ISRN Cardiol* 617943, 2013.

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