Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Case Report

J. Exp. Clin. Med., 2019; 36(2): 59-61
doi: 10.5835/jecm.omu.36.02.005

An unusual case of asymptomatic diffuse alveolar hemorrhage related to amiodarone induced INR elevation

Adem Adar*, **Orhan Onalan**, **Fahri Cakan**

Department of Cardiology, Faculty of Medicine, Karabuk University, Karabuk, Turkey

ARTICLE INFO

Article History
Received 07 / 02 / 2019
Accepted 31 / 10 / 2019
Online Published Date 25 / 12 / 2019

*** Correspondence to:**
Adem Adar
Department of Cardiology,
Faculty of Medicine,
Karabuk University,
Karabuk, Turkey
e-mail: aadar@karabuk.edu.tr

Keywords:
Amiodarone toxicity
Diffuse alveolar hemorrhage
Elevated international normalized ratio

ABSTRACT

Pulmonary adverse effects of amiodarone are among the important causesof morbidity. Such effects may rarely manifest as diffuse alveolar hemorrhage. Another important amiodarone-induced adverse effect is hepatotoxicity. Hepatotoxicity mostly presents as asymptomatic elevation of the liver enzymes. To the best of our knowledge, in amiodarone-induced hepatotoxicity, AST and ALT elevations are well known; however, there are no clear data regarding the high International Normalized Ratio (INR) levels in such a condition. In the present report, we describe the case of a patient under management with chronic low-dose amiodarone, who was admitted to the emergency department for lingual hematoma. During the assessment for bleeding diathesis, the INR was found to be 8.59. After excluding all other possible causes for the high INR level, amiodarone was suggested to be the cause. Since there were diffuse infiltrations on chest x-ray, the patient underwent thorax tomography. Asymptomatic diffuse alveolar hemorrhage secondary to INR elevation was considered. This patient is the first case who had amiodarone-induced INR elevation, and as a consequence, developed asymptomatic diffuse alveolar hemorrhage.

1. Introduction

Amiodarone is one of the anti-arrhythmic medications frequently used in the treatment of ventricular and supraventricular tachycardia. It has a long half-life and accumulates in adipose tissue especially during chronic use (Goldschlager et al., 2007). As with other anti-arrhythmic medications, it has important adverse effects limiting its use and causing increase in morbidity and mortality (Qin et al., 2015). Among these, the commonly known adverse effects are thyroid dysfunction, corneal micro deposits in eyes, blue-looking skin, and toxicity to brain, liver, and lungs (Podrid, 1995). Patients using amiodarone should be monitored regularly for adverse effects (Haverkamp et al., 2017). Here, we report a case of amiodarone toxicity in a 76-year-old male patient presenting with diffuse alveolar hemorrhage and lingual hematoma.

2. Case report

A 76-year-old male patient was admitted to the emergency department with lingual hematoma. He was conscious, cooperative, and his vital signs were stable. On physical examination, he had blue-gray skin discoloration, lingual hematoma (Fig. 1A), corneal micro deposits (Fig. 1B), bilaterally rough inspiratory crackles at the base of the lungs and mild systolic murmur over the left lower sternal border. His medical history involved type 2 diabetes, coronary stent, ICD implantation, and frequent

hospitalization for heart failure. He was taking 60 mg/day gliclazide, 100 mg/day acetylsalicylic acid, 5 mg/day Ramipril, 25 mg/day spironolactone, 0.25 mg/day digoxin and 200 mg/day amiodarone. ECG showed sinus rhythm with left bundle branch block. Transthoracic echocardiography revealed left ventricle systolic dysfunction with an ejection fraction of 25%, moderate biventricular and biatrial dilatation, and mild mitral and moderate tricuspid valve insufficiency. Blood tests on admission showed the following results; Hg, 11.5gr/dL; WBC count, 8.39/mm3; platelet count, 136.000/mm3; glucose, 404 mg/dL; urea, 39.4mg/dL; creatinine, 0.92mg/dL; CRP, 18.89 mg/L; and serum digoxin, 0.9 ng/ml. He was not on any anticoagulant agent and his INR level was 8.59. Bilateral diffuse alveolar density accompanied by diffuse opacities were noted on chest x-ray examination (Fig. 2A). After initial evaluation, he was hospitalized with the suspicion of amiodarone-induced diffuse alveolar hemorrhage. Thoracic computerized tomography (CT) confirmed bilateral diffuse alveolar densities, consistent with alveolar hemorrhage (Fig. 2C). His TSH, T4, and T3 levels were 0.06 IU/mL, 2.10 ng/ dL, and 1.89 pg/mL respectively, suggesting amiodarone-induced thyrotoxicosis. Amiodarone treatment was discontinued, and fresh frozen plasma was administered for high INR levels. Vitamin K administration was found to be ineffective for this purpose. Despite an initial decrease in INR levels after each administration of fresh frozen plasma, his INR levels returned to the baseline levels and remained high during the first ten days. Abdominal ultrasonography revealed no gross abnormality of liver or spleen. All serological and immunological tests, and tests for tumor markers were negative. After discontinuation of the amiodarone treatment, the blue-gray discoloration regressed over days (Fig. 1C). The regression in pulmonary alveolar hemorrhage was demonstrated via chest x-ray (Fig. 2B) and thoracic CT (Fig. 2D). On the 10th day of hospitalization, when INR level was 1.6, the patient was discharged from the hospital. His INR level was within the normal limit one week after discharge.

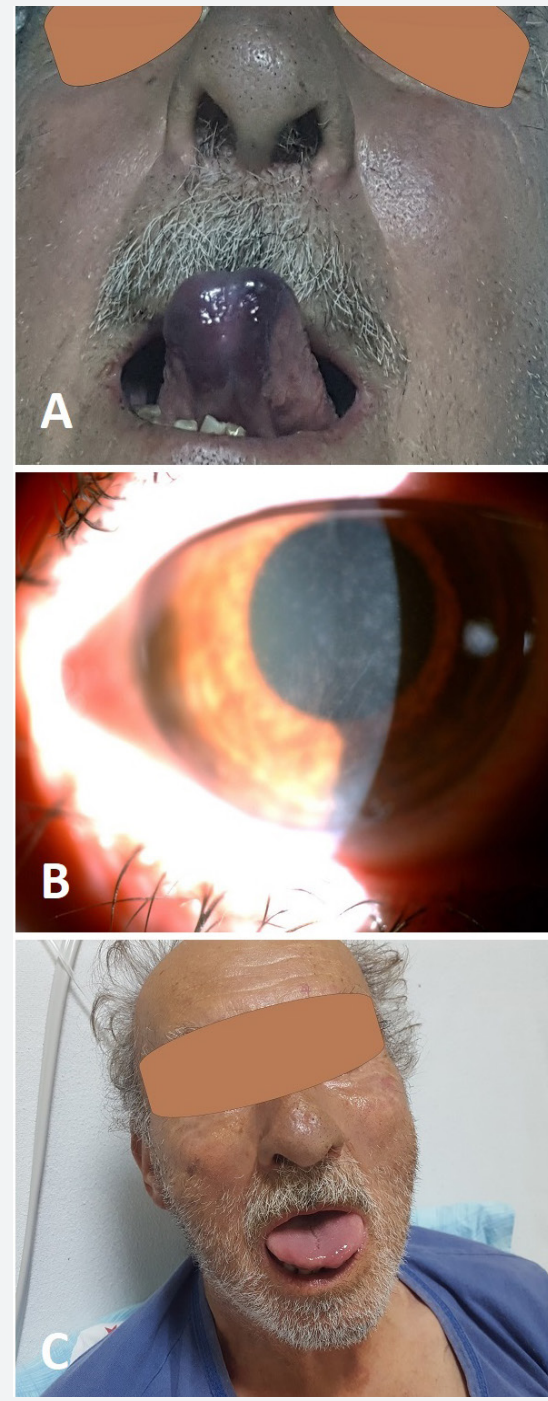

Fig. 1. A. Bluish discoloration, particularly around the mouth and the nose. B. Blue discoloration regressed. C. Corneal micro deposits.

3. Discussion

Patients using amiodarone should be assessed carefully in terms of adverse effects. Hepatotoxicity is a commonly observed adverse effect in patients using amiodarone. It manifests as the elevation of liver enzymes such as AST and ALT. In our case, amiodarone-induced hepatotoxicity manifested as INR elevation without AST or ALT elevation. For hepatotoxicity assessment in patients using amiodarone, it might be useful to check INR levels, in addition to AST and ALT levels.

Due to the lipophilic structure of amiodarone, it has a long half-life varying among patients (35–110 days) (Goldschlager et al., 2007). Therefore, the effects of amiodarone treatment may persist even after discontinuation of the treatment. In the present case, INR elevation persisted for more than 10 days despite multiple fresh frozen plasma administrations. Amiodarone-induced hepatotoxicity was probably the primary reason responsible for the INR elevation in our patient. In addition, INR elevation accompanied by other signs of amiodarone toxicity including those on skin, eyes, thyroid, brain, and lungs were other findings indicating amiodarone-induced INR elevation.

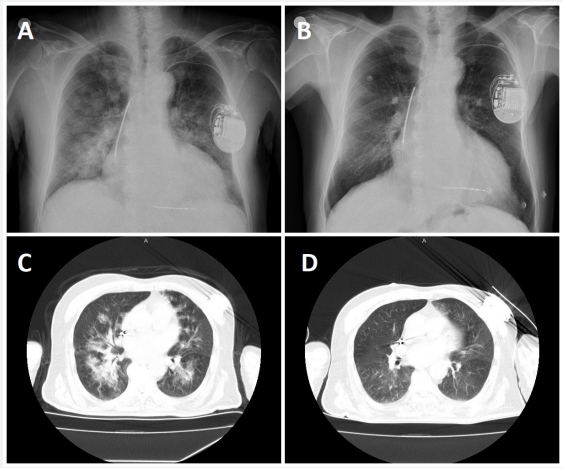

Fig. 2. A. Diffuse alveolar density with diffuse opacities on chest X-ray. B. The regression of pulmonary hemorrhage on chest X-ray. C. Diffuse alveolar density on bilateral lungs on thoracic computed tomography. D. The regression of pulmonary hemorrhage on thoracic computed tomography.

Anticoagulant and anti-platelet medications are frequently used along with amiodarone. In patients taking warfarin, amiodarone-induced INR elevation has been reported in several studies (Lu et al., 2008; Holm et al., 2017). However, in the present case, the patient was not taking warfarin and developed serious INR elevation while using amiodarone. We did not find any other reason for INR elevation. Thus, INR elevation secondary to amiodarone-induced hepatotoxicity was our primary diagnosis. In support of the present case, Sahutoğlu et al. reviewed thyrotoxicosis development and its treatment in a heart-transplant patient using amiodarone. The INR level of the patient, who was using amiodarone, was 32.8 (Sahutoglu et al., 2013). Similarly, in the present case, left ventricle functions were decreased, and the patient developed amiodarone-induced thyrotoxicosis. Decreased left ventricular functions and development of thyrotoxicosis might have been predisposing factors for amiodarone-induced INR elevation in the present case. The patient also used anti-platelet medication (100 mg acetylsalicylic acid). Acetylsalicylic acid use along with elevation of INR levels might have been related to the tongue hematoma and diffuse alveolar hemorrhage, with the effects mediated via increased bleeding risk.

Amiodarone toxicity may be associated with high INR levels and may cause life-threatening bleeding complications like diffuse alveolar hemorrhage. This should always be borne in mind in cases of patients using amiodarone, and INR levels should also be monitored in this context.

REFERENCES

Goldschlager, N., Epstein, A. E., Naccarelli, G. V., Olshansky, B., Singh, B., Collard, H. R., 2007. Electrophysiology. A practical guide for clinicians who treat patients with amiodarone. Heart. Rhythm. 4, 1250-1259.

Haverkamp, W., Israel, C., Parwani, A., 2017. Clinical aspects of treatment with amiodarone. Herzschrittmacherther Elektrophysiol. 28, 307-316. Holm, J., Lindh, J. D., Andersson, M. L., Mannheimer, B., 2017. The effect of amiodarone on warfarin anticoagulation: A register-based nationwide cohort study involving the Swedish population. J. Thromb. Haemost. 15, 446-453.

Lu, Y., Won, K. A., Nelson, B. J., Qi, D., Rausch, D. J., Asinger, R. W., 2008. Characteristics of the amiodarone-warfarin interaction during long-term follow-up. Am. J. Health Syst. Pharm. 65, 947-952.

Podrid, P. J., 1995. Amiodarone: Reevaluation of an old drug. Ann. Intern. Med. 122, 689-700.

Qin, D., Leef, G., Alam, M. B., Rattan, R., Munir, M. B., Patel, D., Saba, S., 2015. Mortality risk of long-term amiodarone therapy for atrial fibrillation patients without structural heart disease. Cardiol. J. 22, 622-629.

Şahutoğlu, C., Pestilci, Z., Kocabaş, S., Zekiye, F.A., Hepkarşı, A., Engin, Ç., 2013. Anaesthetic management in a heart transplantation patient with amiodarone associated thyrotoxicosis. GKD. Anest. Yoğ. Bak. Dern. Derg. 19, 206-210.