UNCOMMON COMPLICATION OF AMIODARONE THERAPY
CASE REPORT AND REVIEW OF LITERATURE

Abdulrahman H. Demerdash, MRCP, UK., Saad Abdullah Shaiban, M.D., Hani Saeed Alzahrani, M.D
Department of Medicine, King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia

Dr. Hani Saeed Alzahrani, M.D
Dept. of medicine, KAUH,
P.O.BOX 9212-23463, Jeddah, Saudi Arabia
Tel, 00966533311888
E-mail: H-SBZ@HOTMAIL.COM

INTRODUCTION
Amiodarone is an antiarrhythmic drug commonly used for treatment ventricular and supra-ventricular arrhythmia, which is associated with multi-organ toxicity. The organs involved include the skin, eyes, liver, peripheral nerves, heart, thyroid gland, and lungs. (1) There are several reports in the literature describing the clinical and histologic features of severe and potentially lethal pulmonary toxicity induced by amiodarone. However, pleural involvement has rarely been described. (1–6)

CASE REPORT
A 84-year-old male referred to pulmonary service due to shortness of breath and dry cough, he is ex–smoker, type 11 diabetes mellitus on metformin 500mg 3times aday, hypertensive on ibrasartan 150mg aday, ischemic heart disease on Plavix 75 mg aday and concor 2.5mg a day, dyslipidemia on simvastatin 20 mg per day, and chronic renal impairment due to diabetic nephropathy, atrial fibrillation on amiodarone 200mg a day for the last year.

On examination, the patient looked well and maintained saturation on room air. His pulse was 76/minute irregular, blood pressure 150/85 mmHg, temperature 37.3C, respiratory rate 16/minute, jugular venous pressure was not raised and normal S1 and S2 no added sound,. There was no pallor or cyanosis. The lung fields revealed reduced air entry and dull percussion note in the left base.

The laboratory investigations revealed a hemoglobin was 11.2 gm% and total leucocyte count and differential were normal. The ESR was 60/mm, C-reactive protein was elevated (3.4 u), while the blood glucose was normal, blood urea 20 mg%, serum creatinine 186 mg%, serum sodium, potassium, and LDH were normal. The liver function test including albumen were normal. Serum lipase and amylase were normal. The tests
for antinuclear antibodies, rheumatoid factor, hepatitis B, and human immunodeficiency virus markers were negative.

A chest radiogram showed moderate left side pleural effusion, otherwise was normal. High-resolution spiral computed tomography (CT) scan of the chest confirmed the presence of left pleural effusion, without intestinal parenchymal changes (Figure 1).

**Figure 1.** Computed tomography scan of chest showing only left-sided pleural effusion.

There was no evidence of pulmonary embolism. CT-guided, left-sided pleural drain was inserted, and 50 mL of yellow slightly cloudy pleural fluid was aspirated. The results of laboratory analysis of the fluid were: RBC - 2335 cells/cmm, WBC 315 cells/cmm (lymphocytes 82%, polymorphs, 1%, mesothelial 3%), protein – 4.3gm/dL, glucose 8.4mmol /dL, and LDH - 181 U/L. The fluid’s Gram’s stain, acid fast stain and cultures were negatives, polymerase chain reaction for acid fast bacilli was also negative and tumor cytology results were all negative. Tuberculin test was >10mm, as the patient had history of smoking, Video-assisted Thorascopics pleural biopsy was arranged, unfortunately the patient refuse the procedure, so we did bronchoscopy which reveals no endo-broncheal lesions, broncho-alveolar lavage from LLL bronchus, cytology was negative for malignancy, gram stain s, acid fast bacilli and culture were negative, polymerase chain reaction for acid fast bacilli was negative. At this stage we started the patient on anti-tuberculous triple therapy, the patient developed drug induced hepatitis in the 1st week, so treatment were stopped, follow up for 15 months the patient did not show worsening of the pleural effusion.
Recently, the patient was admitted through emergency room with non-specific chest pain, and isolated troponin rise, the patient admitted to coronary care unit as decompensated heart failure, as the patient was in sinus rhythm, amiodarone was stopped and the rest of the treatment remained unchanged. Once the patient improved, discharged home for follow up in pulmonary clinic. The next follow up visits after stopping amiodarone, the patient showed marked clinically and radiological improvement and a 2nd chest X-ray, done after 21 days, showed almost resolution of the pleural effusion. (Figure 1).

Hence, our diagnosis was amiodarone - induced pleural effusion without interstitial pulmonary fibrosis.

**DISCUSSION**

In our patient, the exudative picture of the pleural fluid excluded the possibility of heart failure being the cause of pleural effusion. The significant resolution of pleural fluid without any increase in decongestive therapy further excluded the possibility of heart failure related transudate. The leading causes of exudative pleural effusion with lymphocytic predominant are tuberculous, malignancy, pulmonary embolism, collagen vascular diseases, uremia and gastrointestinal tract (GIT) diseases (esophageal
perforation, pancreatitis). Drugs, such as amiodarone, nitrofurantoin and bromocriptine, are also known to induce exudative pleural effusion. In our patient, the absence of growth of tuberculous mycobacteria in the culture excluded pleural tuberculosis. Polymerase chain reaction were repeatedly not detected. In pleural fluid and BAL. The significant reduction in fluid without any antituberculous therapy further excluded this possibility. There was no evidence of pulmonary embolism in the CT scan of the chest. The normal glucose and LDH levels, as well as the absence of rheumatoid factor and antinuclear antibody in the serum, excluded collagen disorder. repeated cytological examination of the pleural fluid did not show any mesothelial or malignant cells, excluding the possibility of metastatic malignancy, mesothelioma and lymphoma. The normal serum lipase and amylase levels and the clinical history ruled out GIT or esophageal perforation as the cause of pleural effusion.

Having ruled out all possible causes of exudative pleural effusion in our patient, we tentatively attributed it to amiodarone drug toxicity. The significant reduction in pleural fluid and the symptomatic relief felt by the patient after the drug was discontinued supported our hypothesis.

Amiodarone-induced Pleural Toxicity

Pleural abnormalities associated with amiodarone therapy are uncommon and have been described as incidental finding on chest radiogram, usually in association with fibrosing alveolitis, (2)

We summarized the reported patients, all patient with pleural effusion had concomitant parynchemal involvement, all patients with pleural abnormalities had been on therapy with moderately high maintenance dose of amiodarone (>400 mg /day, and had been on drug therapy from 4-24 months.

We found 3 cases where pleural effusion were noted in association with amiodarone therapy, 1st Dar-mata et al reported a 68 years old man with poor LVF after AMI who developed respiratory insufficiency and RT side pleural effusion ,,the fluid was not characterized ,the patient had no other systemic finding associated with amiodarone toxicity , subsequently the patient died from cardiopulmonary failure (4).SOBOL and RAKITA reported a 40 years old female with pulmonary stenosis on procainamide ,phenytoin, tocainide and propranolol in addition to amiodarone ,developed fever and right side pleural effusion and right pulmonary infelterate(5). CLARKE et al reported a 29 years old man with refractory supraventricular tachycardia after 10 months of therapy with quinidine and moderately high maintenance dose of amiodarone ,the patient developed pleural and pericardial effusion .while it is likely that in two of these cases the pleural effusion were temporally associated and related to amiodarone therapy
these patients concomitantly taking other medication such as procainamide, quinidine and phenetoin which can also cause pleura-pulmonary reaction (6).

In the case by dar-mata et al the patient was post MI and poor LVF, in neither of the other cases could the diagnosis of congestive heart failure be completely excluded, in contrast to our patient, who had exclusively Lt sided pleural effusion with pleural thickening, without parenchymal involvement which is never reported before particularly with relatively small maintenance dose of amiodarone. The drug was started 6 months before developng pleural effusion, an extensive workup excluded other resonable possibilities to explain our finding, upon withdrawal of amiodarone the pleural effusion resolved completely over 2months, further supporting the causative role of amiodarone in the process consider it exclusively due to amiodarone therapy. in addition to significant improvement in renal profile after discontinuation of amiodarone.

Most reports amiodarone lung toxicity emphazise the association of lung fibrosis, and drug information does not insert the pleural side effect.

Our report illustrate the unusual pleura-pulmonary manifestation of amiodarone toxicity that should alert the clinicians, as this association not been suffiently has previously emphazised. 

A review of the literature shows that when pleural effusion occurs as a manifestation of amiodarone toxicity, concomitant parenchymal involvement is usually present. There is a single case report of amiodarone- associated pleural effusion without parenchymal involvement.( 3 )  In this case, however, a chest x-ray, which does not have the sensitivity to detect early pulmonary involvement, was used to exclude pulmonary toxicity. High-resolution computed tomography is far more superior to plain chest x-ray for the early detection and confirmation of interstitial lung disease. A review of the reported cases also suggests that the occurrence of pleural toxicity had no relation with the age of the patient, underlying arrhythmia, cardiac functions, or the dosage of medications and duration of therapy.

Pleural effusion can be bilateral in some cases and confined to either side in others, and its extent may be massive. The exudate is always rich in proteins, RBCs and mononuclear cells. The analysis of the pleural fluid, however, does not lead to any specific diagnostic finding. A few workers have reported the presence of foamy
macrophages, but the presence of these cells is not diagnostic because they are often found in cases of lipid storage disorders and in patients taking amphilic drugs, such as anorectics, neuroleptics, antihistaminic and tricyclic antidepressants.

CONCLUSION
Amiodarone-induced pleural effusion is rare, but if this possibility is not considered, the patient may undergo unnecessary, costly investigations and even wrong empirical management. Drug induced pleural effusion should be considered in any patient using amiodarone. This is a potentially reversible cause of exudative pleural effusion. Periodic evaluation by CXR and, if possible, CT scans of the chest can facilitate early detection of the condition. Discontinuation of amiodarone usually reverses the toxicity. Some patients who do not respond to discontinuation of the drug may need steroids.

REFERENCES


