Amiodarone Induced Interstitial Lung Disease: An Enigma

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ABSTRACT

Amiodarone is an anti-arrhythmic drug that has potential to cause Interstitial Lung Disease (ILD) commonly non-specific Interistitial pneumonia. We present a 75-year male presenting with gradual onset progressive shortness of breath and dry cough after undergoing coronary artery bypass grafting (CABG) and was kept on amiodarone therapy post-surgery to control arrhythmias. The patient was diagnosed as amiodarone induced Non-Specific Interstitial Pneumonia (NSIP) after excluding alternative diagnosis. Early recognition and stoppage of amiodarone, prompt treatment with corticosteroid and respiratory support had favorable clinical outcome in this case.

Keywords: Amiodarone; Interistitial Lung Disease; Non-Specific Interistitial Pneumonia

INTRODUCTION

Interstitial Lung Diseases (ILD) are heterogenous group of disorders that affect lung parenchyma, alveoli and/or airways. Most identifiable causes are due to environmental and occupational exposure, radiation and drug induced.[1] Three percent of ILD are due to drug induced, among them 10% are due to amiodarone which may be fatal.[2] Pulmonary toxicity of amiodarone depends with prolonged exposure to high dose of amiodarone in older age patient with pre-existing lung diseases.[3] As amiodarone is a commonly used drug and has propensity to cause NSIP pattern of ILD, so we present a case report of amiodarone induced ILD.

CASE

A 75-year male, reformed smoker, known case of hypertension, symptomatic coronary artery diseases involving stenosis of 80-90% in left anterior descending artery and 99% in left circumflex artery on angiography. Thus, he underwent CABG following which he was started on aspirin, clopidogrel, metoprolol succinate, furosemide and rosuvastatin. Along with these medications, amiodarone 800 mg per day in four divided doses was started for ventricular arrhythmias post surgically and was discharged.

After 1 month of CABG, patient presented to our hospital with history of shortness of breath which was gradual onset, exertional, progressive from mMRC grade 1 to grade 4 associated along with dry cough for one week. Case was referred from Cardiovascular Thoracic Surgery (CTVS) department to our, Pulmonary, Critical Care and Sleep Medicine (PCCSM) department in view of requiring pulmonologist care. On further evaluation, the patient didn't have any prodromal symptoms suggestive of viral illnesses, neither of other lower respiratory tract infections. The dyspnea didn't accentuate on recumbent position, nor was history suggestive of paroxysmal nocturnal dyspnea. There was no clinical symptoms and signs suggestive of connective tissue diseases like rheumatoid arthritis, systemic sclerosis, Sjogren syndrome, mixed connective tissue disease.

On presentation he had a blood pressure of 100/60 mmHg, a regular heart rate of 86 beats/min [under beta-blocker], a respiratory rate of 30 breaths/min, and peripheral arterial oxygen saturation (spO2) of 84% at 8 to 10L/min of oxygen via face mask. On chest examination, there was bilateral vesicular breath sound with equal air entry and fine crepitations were heard over bilateral infra-axillary and infra-scapular regions. Other systemic examinations were unremarkable.

Laboratory workup showed normal parameters except for elevated CRP level. [hemoglobin of 12.7 gm/dl, white blood cell count (WBC) 8990 cells/UL with 73% neutrophils, platelets 166000 per cc, urea 30 mg/dl, creatinine 0.46 mg/dl, aspartate aminotransferase (AST) 24.42 U/l, alanine aminotransferase (ALT) 26 U/l, alkaline phosphatase (ALP) 128.22 U/l, total protein 5.89 gm/dl, serum sodium 135.5 mmol/L, potassium 4.1 mmol/L and C-reactive protein (CRP) 96 mg/L.]

With those initial presentations and evaluations, differential diagnosis of left ventricular failure, lower respiratory tract infection, Pulmonary Embolism, Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Drug induced ILD was made and evaluated further.

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On initial chest radiograph there were bilateral diffuse hazy opacities (ground glass opacities) along with linear opacities, without predominant perihilar infiltration and peri bronchial cuffing (Figure 1.A).

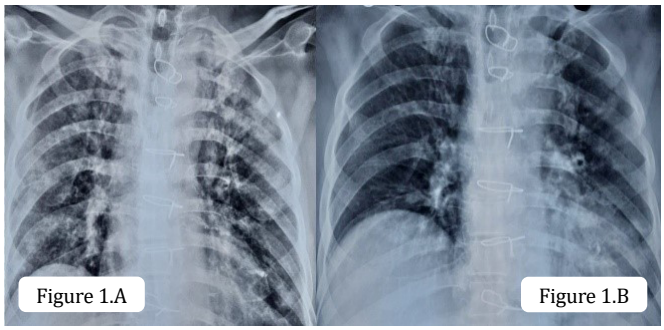
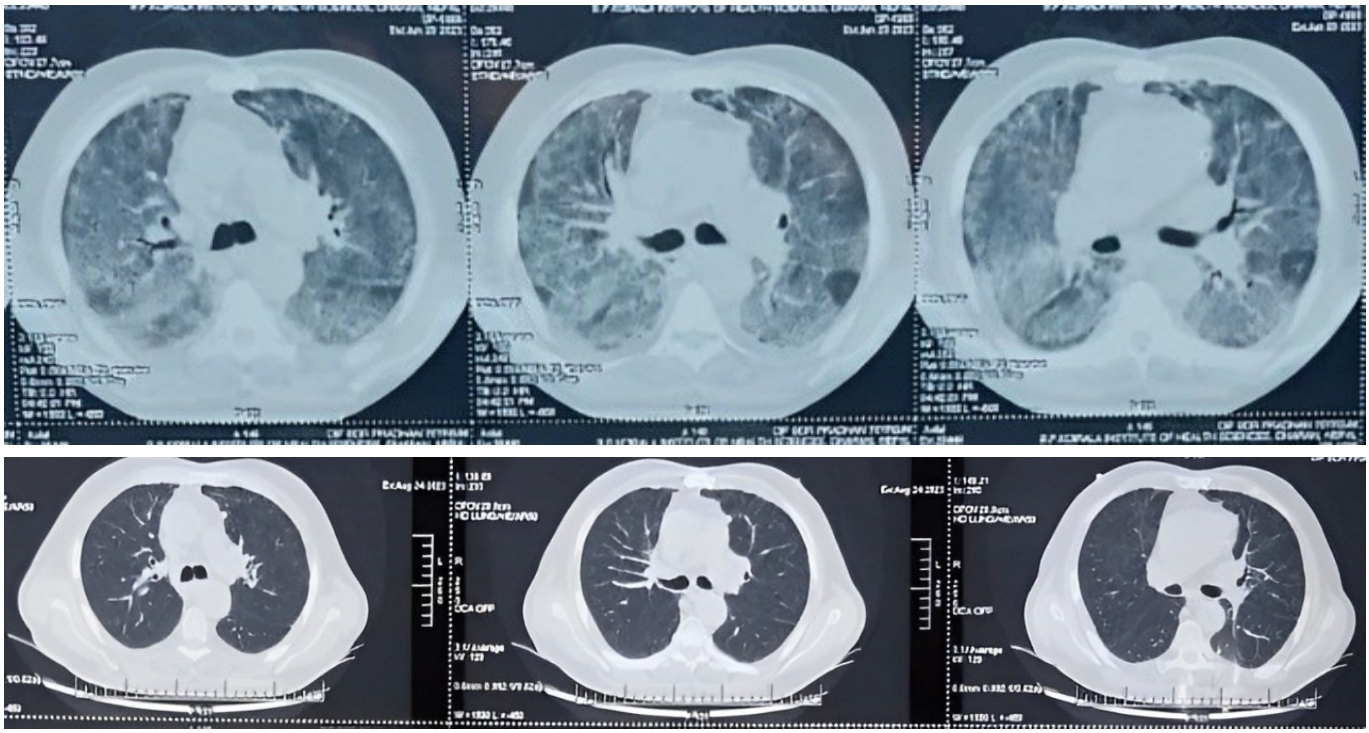


Figure 1: Comparing chest x-ray at initial presentation (1.A) and on follow up at 2 months (1.B) showing clearing of lung field without ground glass opacities (GGO)



Chest computed tomography (CT) scan was performed at the time of presentation which showed bilateral symmetrical and diffuse GGO, with subpleural sparing and interlobular septal thickening without honeycombing suggestive of NSIP (Figure 2A).

With all the above clinico-radiological correlation, we kept the working diagnosis as amiodarone induced NSIP, for which abrupt stoppage of the culprit drug was done. Despite which, we tried our best to rule out other possible differentials. Thus, Sputum work-up for Gram stain, culture along with AFB, Xpert MTB/RIF yielded negative result. Bronchoalveolar lavage couldn't be performed due to the patient's distress and high oxygen requirement at the time of admission.

On further investigation, Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (anti-CCP), Anti-Neutrophil Antibody (ANA) along with ENA pannel came out to be negative.

Considering the patient's severity of respiratory distress and lung involvement, patient was treated with pulse therapy of methylprednisolone for the first three days. To correct patient's hypoxia and to decrease work of breathing, he was kept initially on Non-Invasive Ventilation with PEEP support followed by High Flow Nasal Cannula (HFNC). Patient gradually improved during the course of hospital stay and was discharged after 5 days of admission in PCCSM ward with oxygen via nasal prong 1liter/ minute, with methylprednisolone with 32 mg/day for the first 2 weeks and then tapering to half the initial dose every two weeks then stopped over 2 and ½ months.

On a follow up visit after 1 month, patient respiratory symptoms and chest imaging were improving but patient used to desaturate during exertion and in two months of follow up, patient was free from oxygen support without respiratory symptoms. Chest imaging findings in two months follow up were near normal without areas of hazy opacities (Figure 1.B). Features of NSIP pattern of ILD on CT scan of the chest had resolved showing only few areas of intralobular pleural thickening (Figure 2B). Spirometry performed on follow up was normal with FEV1/FVC: 0.76, FEV1: 82% of predicted, FVC: 86% of predicted.

DISCUSSION

Amiodarone is an class III anti-arrhythmic drug which acts by blocking potassium channels, mainly used for management of supraventricular as well as ventricular arrhythmias. It causes several adverse effects among which pulmonary toxicity is

a serious side effect of amiodarone, which can cause various pulmonary diseases like interstitial pneumonitis, eosinophilic pneumonia, ARDS, and others, with interstitial pneumonitis being the most common. Symptoms typically begin within 6 to 12 months of starting low dose (<400 mg/day) of amiodarone but they can also appear as early as two months or take several years to develop.[4] Interstitial pneumonitis often develops after over two months of amiodarone treatment, especially with doses above 400 mg daily.[5] Our patient was started on a higher dose i.e., 800 mg/day of amiodarone post CABG and presented with symptoms within one month of starting the drug. A. J. Sweidan et al. reported a case where 800mg/day was used similar to our case and patient developed symptoms in 3 months[6]. Additional risk factors include extended therapy duration, older age, preexisting lung conditions and recent pulmonary angiograms. Amiodarone-induced interstitial pneumonitis is believed to be due to either direct toxic injury to lung cells or an indirect immunologic reaction. The drug's high tissue affinity for the lung lead to the accumulation of drug-phospholipid complexes in lung cells, causing cellular injury and death, while the presence of lymphocytic infiltration and other immune features in some patients suggests a hypersensitivity pneumonitis component.[7]

Amiodarone-induced interstitial pneumonia is diagnosed by ruling out other causes of interstitial pneumonia, left ventricular failure and infectious diseases. If the clinical signs and evaluations align, other conditions are excluded, and the patient's condition improves after stopping the drug, with or without glucocorticoids, a clinical diagnosis is often made. We took a similar approach for our case where we stopped the drug and started the patient on methylprednisolone and ruled out other causes of interstitial pneumonitis. The patient's condition improved in two months. C. E. Mitrofan et. al reported a case where they treated the patient with methylprednisolone 16 mg/ day tapering over three months with improvement of dyspnea, chest and computed tomography.[8] In this case, patient had severe dyspnea of MMRC grade 4 along with dry cough after 1 month of high dose of amiodarone therapy after cardiac surgery. Chest imaging showed severe form of non- specific interistitial pneumonia with bilateral diffuse involvement. Case was managed with non-invasive ventilation and HFNC initially to support for severe dyspnea and hypoxia along with high dose of corticosteroid and stopping of amiodarone, which help in restoration of lung function and favorable clinical outcome.

CONCLUSION

Amiodarone can cause life threatening pulmonary toxity presenting as interistial lung disease usually nonspecific interistial pneumonia pattern as in this case. Patient on prolonged duration of amiodarone with dose ≥ 400 mg/day, who presents with acute or progressive shortness of breath along with dry cough and diffuse hazy areas of opacities should be evaluated for pulmonary toxity of amiodarone with HRCT chest and pulmonary function test as well as to evaluate other systemic toxicity. Early recognition and treatment with systemic corticosteroid and withdrawal of amiodarone has favorable clinical outcome.

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