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Clinical Case Seminar **CCS1 (1-5)**

A case of fibrosing interstitial pneumonia

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Abstract

We report here the case of a 70 year-old male, lifelong never smoker, who has been admitted to our inpatient Pulmonology clinic for the presence by one month of persistent fever associated in the last seven days with fatigue and mild exertional dyspnea (2 at the Borg scale). An arterial blood gas analysis performed during oxygen therapy [fractional concentration of oxygen in inspired gas (FiO2) of 40%] showed the presence of an acute hypoxemic respiratory failure. He had a past medical history of paroxysmal atrial fibrillation treated in the last two years with low-dose amiodarone and edoxaban. High-resolution computed tomography of the chest showed a bilateral, but with the prevalence in the right lung, pattern of interstitial lung disease with diffuse ground glass opacities with high attenuation, interstitial thickening, traction bronchiectasis and honeycombing. A diagnosis of amiodarone-induced pulmonary fibrosis was done and the drug was stopped and replaced with bisoprolol and concomitant treatment with systemic glucocorticoids for two weeks was started. The patient was discharged at home without respiratory failure. The patient died five months later in the Pulmonology clinic "Vittorio Emanuele" University Hospital of Catania, Italy during another acute exacerbation of its disease.
Our report is a reminder for clinicians to recognize that even low-dose amiodarone (200 mg/daily) may be associated with severe pulmonary fibrosis. There is a complete absence of a standardized approach to the diagnosis and treatment of this disease.

Key Words: amiodarone; pulmonary toxicity; interstitiallung disease; pulmonary fibrosis

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Introduction

Amiodarone-induced pulmonary fibrosis is the most serious and a potentially life-threatening adverse reaction of amiodarone and one of the leading causes for discontinuation of the drug (1), however several forms of pulmonary injury may occur in patients treated with amiodarone (table 1). Diagnostic criteria for amiodarone-induced pulmonary injury are not available as well as standardized treatment, prevention and follow up recommendations (1).

Tab.1 Summary of amiodarone-induced pulmonary injury

Interstial lung diseases	**Common:** eosinophilic pneumonia, organizing pneumonia, pulmonary fibrosis.
Lung nodule (s) or mass	**Rare**
ARDS	**Rare**
DAH	**Rare**
Airway disease	Asthma-like bronchoconstriction and cough (rare)
Pleural involvement	**Common** Pleural thickening **Rare** Pleural effusion, drug-induced lupus
Pulmonary vascular diseases	Thromboembolic disease, pulmonaryarterialhypertension

ARDS: Acute respiratory distress syndrome**; "DAH**: Diffuse alveolarhemorrhage yndrome"
Obtained with the data from the references 4,6,8 and www.pneumotox.org

Case presentation

A 70-year-old male (178 cm, 78 kg, body mass index 24 Kg/m^2), lifelong never smoker, Caucasian, railroad worker retired by 15 years presented at the emergency department of our University Hospital "G. Martino" of Messina, Italy (www.polime.it) for the presence by one month of persistent fever associated in the last 7 days with fatigue and mild exertional dyspnea (Borg scale 2). At the emergency department the patient performed a chest x-ray that showed the presence of diffuse pulmonary opacities in the right lung parenchyma (Figure 1A) and after an outpatient visit in our pulmonology clinic was discharged with a treatment prescription of oral amoxicillin/clavulanic acid. After 4 days, the patient returned in our emergency department for the persistence of the above symptoms. At this point the patient was admitted to our inpatient clinic. His past medical history was characterized by paroxysmal atrial fibrillation treated in the last two years with oral amiodarone (200mg/daily) and edoxaban (60 mg/daily). He was under regular treatment by 15 years with oral alprazolam (1 mg/daily) for an anxiety-depressive disorder. At the admission his vital signs were (Table 2): systemic blood pressure 95/70 mmHg, pulse frequency of 57/min (rhythmic), body axillary temperature of 37.1°C, respiratory rate of 20 breaths per minute, oxygen saturation value of 92% when breathing room air. An arterial blood gas analysis (ABGA) performed with oxygen therapy with Venturi mask at a fractional concentration of oxygen in the inspired gas (FiO_2) of 40% showed: pH 7.44, arterial partial pressure of oxygen (PaO_2) 86 mmHg, arterial partial pressure of carbon dioxide ($PaCO_2$) 38 mmHg. Physical examination of the chest revealed bibasilar "velcro-like" inspiratory crackles. No other physical signs outside the chest were pathological. Routine laboratory tests showed: leukocytosis with neutrophilia [total leukocyte 15200 cell/mm3 (normal range 4500-9000), neutrophils count 12160 $cell/mm^3$ (normal range: 1500-7700 $cell/mm^3$) and slight increase of the serum C-reactive protein level [1 mg/dl (normal range:0-0.50 mg/dl)]. Serum thyroid hormones were normal [free triiodothyronine 2.14 pg/ml (normal range: 2-4.4), free thyroxine 22.4 pmol/L (normal range:12-22); thyroid-

stimulatinghormone1.930μUI/mL (normal range:0.270-4.2).

Pre-bronchodilator spirometry showed a suspected restrictive pattern [forced expiratory volume in one second (FEV_1): 1,74 L (56% of the predicted values), forcedvitalcapacity (FVC): 2,31 L (57% of the predicted values), FEV_1/FVC ratio 83% of predicted]. Unfortunately, the patient was not able to perform an acceptable maneuver to measure static lung volumes and the diffusing capacity for carbon monoxide.

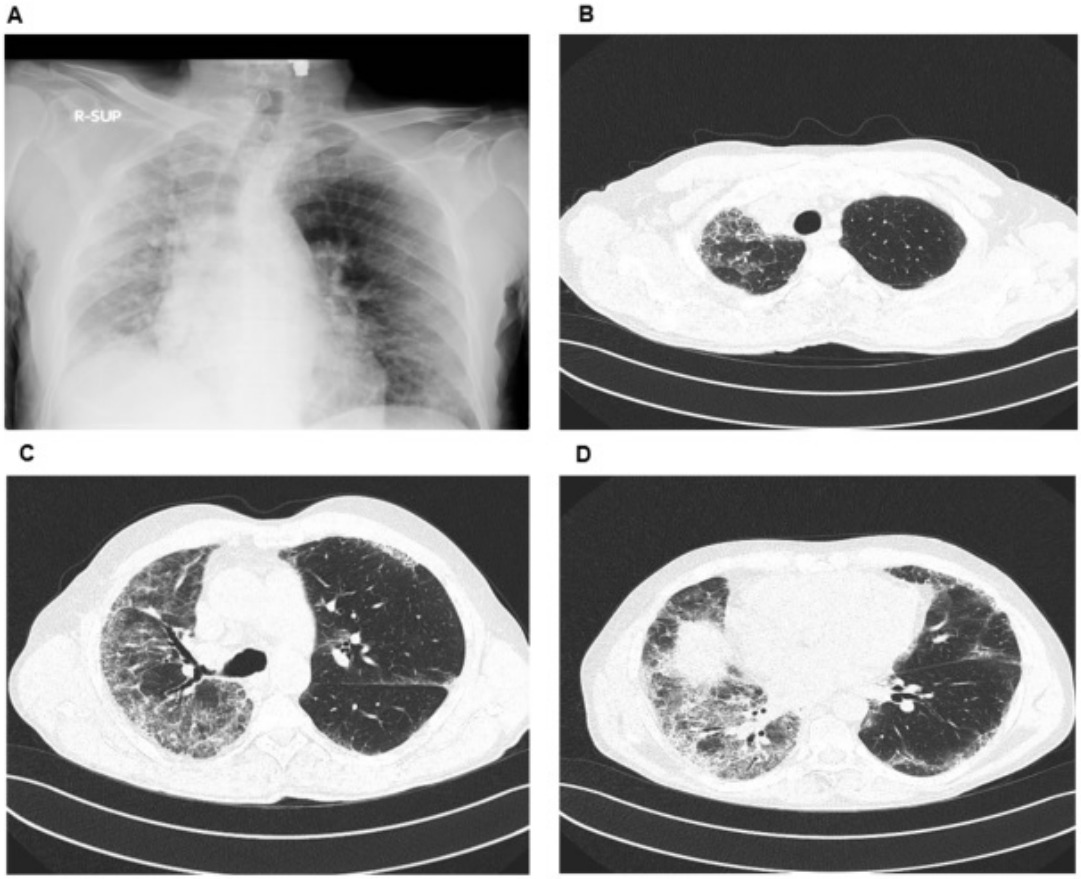
Tab.2 Summary of the clinical, laboratory and functional parameters

Clinical parameters	
Systolic blood pressure	**95 mmHg**
Diastolic blood diastolic pressure	**70 mmHg**
Respiratory rate	**20/min**
Pulse rate	**57/min**
Oxigen saturation	**92%**
Axillary temperature	**37.1°C**
Laboratoryparameters	
WBC (4500-9000 cell/mm^3)	**15200 cell/mm^3**
Neutrophils (1500-7700 cell/mm^3)	**12160 cell/mm^3**
Serum CRP (0-0.50 mg/dl)	**1 mg/dL**
Pre-bronchodilator spirometry	
FEV_1	**1,74 L (56% of the predicted value)**
FVC	**2,31 L (57% of the predicted value)**
FEV_1/FVC ratio	**83% of predicted**
Arterialbloodgasesanalysis, performed with oxygen therapy with Venturi mask at a FiO_2 of 40%	
pH (7.35-7.45)	**7.44**
$PaCO_2$ (35-45 mmHg)	**38 mmHg**
PaO_2 (80-100 mmHg)	**86 mmHg**
Serum bicarbonates (22-26 mmol/L)	**24 mmol/L**
SaO_2 (94%-100%)	**98%**
Functionalparameters	**FEV1, FVC e FEV1/FVC ratio**

CRP: C-reactive protein; FiO_2: fractional concentration of oxygen in the inspired gas;FEV_1: forced expiratory volume in one second; WBC: white blood cells; FVC: forced vital capacity.

High-resolution computed tomography of the chest (HRCT) showed a bilateral, but with the prevalence in the right lung, pattern of interstitial lung disease with diffuse ground glass opacities, interstitial thickening, traction bronchiectasis and honeycombing (Figure 1,panel B, C, D). The HRCT pattern was consistent with a diagnosis of amiodarone-induced pulmonary fibrosis (2). Therapy with amiodarone was stopped and replaced with bisoprolol 2,5 mg/daily and a therapy with systemic glucocorticoids (prednisone 25 mg/daily) was started for 15 days. After 4 days the fever has disappeared. Another ABGA performed in breathing room air 4 days after amiodarone discontinuation showed the presence of mild hypoxemia: pH 7.43, PaO_2 75 mmHg, $PaCO_2$ 34 mmHg, SpO_2 95%. After 15 days the patient was discharged. He did not present at the follow-up visit. The patient died five months later in the Pulmonology clinic “Vittorio Emanuele” University Hospital of Catania, Italy during another acute exacerbation of its disease

Fig.1. (A) Chest x-ray (performed on supine position) 4 days before hospital admission showing the presence of diffuse pulmonary opacities in the right lung parenchyma. (B, C, D) High-resolution computed tomography of the chest performed at the admission in our Pulmonology inpatient clinic, showing a bilateral, but with the prevalence in the right lung, pattern of interstitial lung disease with diffuse ground glass opacities, interstitial thickening, traction bronchiectasis and honeycombing.



Discussion

Amiodarone is a class III-antiarrhythmic, iodinated lipophilic drug with a long half life (40-70 days) and accumulation in several tissues (such a thyroid and lung) (3). The incidence of amiodarone pulmonary fibrosis is 2.1% per year in patients taking ≤ 200 mg/daily (4). Potential risk factors include increased patient age, preexisting lung disease and thoracic or non-thoracic surgery (1). Cumulative dose exposure of amiodarone is commonly considered a risk factor however no safe dose has been ever established and serious side effects of amiodarone can occur even at low dosage (5).

The mechanisms involved in amiodarone-induced pulmonary fibrosis are incompletely understood. Two major hypotheses have been suggested, including a direct toxic injury to lung cells and triggering of an autoimmune response (3). There are no specific diagnostic criteria of amiodarone-induced pulmonary fibrosis, that requires exclusion of alternative causes. Laboratory findings are nonspecific (3). Spirometry usually reveals a restrictive pattern typically associated with reduced DLCO (6). In contrast of other drug-induced lung fibrosis, amiodarone-induced pulmonary fibrosis is usually characterized in the high-resolution computed tomography of the chest by an asymmetrical pattern (with the right lung more frequently involved) (2). Parenchymal pulmonary infiltrates that have a high attenuation are typical.

Ground glass opacities are seen frequently and may be an early finding. Bibasal reticular opacities and traction bronchiectasis suggest the presence of pulmonary fibrosis (3). Bronchoalveolar lavage fluid examination is not diagnostic, but may be present lipid-laden macrophages (3). Open lung biopsy is usually not performed due to the high risk of ARDS and death. Treatment consists of immediately discontinuing the drug (3). Unfortunately there are no standardized clinical recommendations for the duration and dosing of the treatment with systemic glucocorticoids, that is considered appropriate on severe cases (extensive involvement on chest imaging and the presence of respiratory failure) (1). The mortality is highest among the patients with pulmonary fibrosis (1). Patients hospitalized with amiodarone pulmonary fibrosis have a mortality at day 90 of 37% (7). Before the beginning of a require amiodarone treatment the patients should have an initial chest x-ray, a regular clinical evaluation and pulmonology consultant with spirometry, including DLCO (2). However, there are not standardized guidelines on the follow-up visit but may be recommended every 3 months during the first year of the treatment with the drug and, subsequently every 6 months or when this patient develop respiratory symptoms (1).

Conflicts of interest: The authors declare no conflict of interest.

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