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Amiodarone-induced pulmonary toxicity: case series and review of clinical-radiological correlations

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Abstract

Amiodarone is an effective and commonly used anti-arrhythmic drug. The radiographic presentations of amiodarone-induced pulmonary toxicity (AIPT) include a broad spectrum of patterns. Three main clinical-radiographic presentations are described with AIPT: isolated reduction of diffusing lung capacity with no clinical implications; alveolar-interstitial pneumonia, which usually requires amiodarone discontinuation and corticosteroid treatment; and acute respiratory distress syndrome, which can obviously be life-threatening.

We report 6 cases that depict the described range of clinical and radiographic presentations. The analysis of the cases and of the published review suggests that the computed tomography scan pattern on presentation predicts well the clinical course. The correlation between radiographic and clinical findings can therefore guide the clinician in the management of AIPT.

Key words: amiodarone, drug-induced lung toxicity, CT scan pattern, interstitial pneumonia, organizing pneumonia, acute respiratory distress syndrome.

Introduction

Amiodarone is a benzofuranium derivative (with 37% iodine) originally indicated as a smooth muscle relaxant and coronary vasodilator for the treatment of angina pectoris. In 1968, amiodarone was approved by the Food and Drug Administration (FDA) for the treatment of malignant ventricular arrhythmias [1]. Currently, amiodarone is still widely used in hyperkinetic arrhythmias refractory to common antiarrhythmics and in ventricular preexcitation syndromes [2]. Since 1972, a number of side effects have been in fact attributed to amiodarone, including skin photosensitization, peripheral neuropathies, thyroid abnormalities (hyper and hypothyroidism), corneal microdeposits, liver and gastrointestinal disorders, and interactions with other cardiac medications [3-5].

The first data on the possible amiodarone-induced pulmonary toxicity (AIPT) date back to 1980, and were appropriately described as "interstitial pneumonia" [1]. Following the first report, it was later recognized that AIPT is the most serious, and sometimes fatal, adverse event associated with the use of this drug [1,6]. The diagnosis of AIPT is by exclusion of other causes of new pulmonary infiltrates [7]. The incidence of AIPT is between 2 and 4%, according to contemporary studies [8-11]. Although some dose-response relation with amiodarone use and development of AIPT was found [9], substantial pulmonary toxicity can be observed even with small maintenance doses (100-200 mg) [10-11]. Across published studies, the main risk factor for AIPT is the older age of the patient [9,11-13].

The primary mechanism of action of amiodarone involves the inhibition of potassium rectifier currents responsible for repolarizing the heart during phase 3 of the cardiac action potential. This potassium channel-blocking effect results in increased action potential duration and a prolonged effective refractory period in cardiac myocytes [14]. Amiodarone also blocks, albeit to a lesser extent, the sodium and calcium channels and is a powerful antiadrenergic drug, exerting a non-competitive blockade on both beta and alpha receptors [14]. Higher concentrations of amiodarone are seen in organs with high lipid content such as adipose tissue, lungs, liver and thyroid [15]. The metabolite N-desethylamiodarone can reach concentrations 5 times higher than amiodarone itself, therefore acting as a sustained release reservoir. This explains the delayed onset of amiodarone toxicity, even after discontinuation of the drug [16].

A variety of clinical presentations and radiographic patterns have been described with AIPT. The purpose of this article is to review, through a detailed case series and analysis of the literature, the radiographic patterns of AIPT and to establish possible correlations with the clinical courses.

Clinical, radiologic and pathologic patterns of AIPT

AIPT represents a classic example of drug-induced lung toxicity which can be defined as "the pathological state that is determined in the lung parenchyma as a result of pharmacological substances of clinical-therapeutic use" [17]. The clinical-radiographic-pathologic presentations of AIPT can be divided into 3 main categories [18].

Mild, isolated and asymptomatic impairment of the diffusion capacity of the pulmonary alveolar-capillary membrane

Many patients receiving amiodarone therapy present an isolated reduction in carbon monoxide diffusion capacity (DLCO) (<15-20% compared to baseline) [18]. This phenomenon, in itself not really an indication of toxicity, but simply exposure to the drug, is attributable to the increased lung phospholipid content induced by amiodarone, due to inhibition of lysosomal phospholipase A1 [13] with multilamellar lysosomal inclusions found in several lung cells, such as macrophages. The amiodarone-induced phospholipidosis causes a foamy cell response involving type II pneumocytes, endothelial cells and other interstitial resident cells (lipoid pneumonia). The foamy cells occupy space and reduce the effective surface for gas exchange, but it may not lead to any clinical consequence, other than the detectable DLCO reduction [16]. Radiographically, there are no reported changes with the isolated DLCO reduction following amiodarone exposure [17-22]. In these cases, in the absence of new opacities on the chest CT scan, amiodarone discontinuation is not required.

Alveolar-interstitial pneumonia

The majority of clinically significant cases of AIPT are represented by an alveolar-interstitial pneumonia. The main pathologic patterns of alveolar-interstitial pneumonia in AIPT are represented by organizing pneumonia (OP) [23] and nonspecific interstitial pneumonia (NSIP). In these case, actual damage occurs and it is caused by an increase of pulmonary surfactant due to increased production, induced by amiodarone, by type II pneumocytes [19]. In such cases, the clinical onset is subacute, with nonproductive cough, progressive dyspnoea on exertion and, less frequently, low-grade fever, malaise and weight loss [16].

Organizing pneumonia in AIPT, as in different etiologies, presents on chest x-ray as patchy, often peripheral areas of consolidation, typically bilateral and located in the lower lung fields [18,24,25]. On the chest CT scan, OP presents as peripheral or peribronchial airspace opacities,

typically patchy and non-segmental, predominantly located in subpleural or peribronchial regions. These consolidations are often accompanied by adjacent ground-glass opacities ("halo sign"), reflecting a mixed pattern of alveolar and interstitial involvement. Another possible radiologic feature is the "reversed halo sign", characterized by a central ground-glass opacity encircled by a denser rim of consolidation. In many cases, air bronchograms (air-filled bronchi visible within areas of consolidation) are observed, further indicating the presence of alveolar filling [26]. Given that OP has to be biopsy-proven in order to be diagnosed and distinguished from infection-induced airspace opacities with certainty, the real incidence of OP in AIPT may be underestimated.

Clinically, patients with OP type of AIPT present acutely with dyspnea, fever, pleuritic chest pain and rapid worsening [27]. Some authors actually claim that an early detection of OP component by transbronchial biopsies may be important, as the early institution of corticosteroid treatment can reduce mortality from about 50 to 15% [19,21-23,28]. On the other hand, corticosteroid treatment would be used for any (suspected or certain) clinically significant presentation of AIPT. We argue that, in the presence of biopsy-proven OP, a higher dose (0.5 mg/kg) may be used for 6-8 weeks continuously.

Patients with true AIPT can alternatively present with a NSIP pattern, characterized by varying degrees of interstitial inflammation and fibrosis. Findings on the chest x-ray include diffuse reticular opacities, usually more prominent in the lower lung zones, while chest CT shows diffuse or patchy ground-glass opacities, but lacking the sharply defined consolidation typical of organizing pneumonia. Fine reticular opacities, representing interstitial thickening, are often more pronounced in the lower lobes, and subpleural sparing is a characteristic feature. The presence of traction bronchiectasis indicates fibrotic changes. The NSIP pattern of AIPT typically presents symmetrically, affecting the lower lung fields [29]. Clinically, with the NSIP pattern of AIPT, patients experience a gradual onset of dyspnea, non-productive cough, weight loss, and, only occasionally, fever. This subacute clinical picture can persist for weeks or months.

Organizing pneumonia is frequently associated with AIPT, and it is steroid-responsive, usually with good outcome [21].

The reported mortality rate of the alveolar-interstitial pneumonia in AIPT is 5-20% [6,30]. However, this rate may be overinflated by the inclusion of more severe cases (see next section) in older studies.

Acute respiratory distress syndrome

The acute respiratory distress syndrome (ARDS) manifestation of AIPT has been described, even after a brief period of exposure to amiodarone, often as a postoperative complication of cardiac surgery for malignant ventricular arrhythmias [31], general surgery [32], thoracic surgery [33], after a coronary angiography [34], or in the course of acute renal failure or sepsis [35]. In these cases, the onset is acute [36]. Evidently, the ARDS presentation of AIPT prevalently occurs when the patient is more vulnerable to serious respiratory complications, due to post-operative stress or other organs' failure. Alternatively, AIPT can evolve to ARDS when it is recognized late [37].

As for other types of ARDS, this AIPT presentation is a serious condition characterized by acute hypoxemic respiratory failure with rapid progression, often requiring mechanical ventilation [38]. The finding of lipid-laden macrophages was described on bronchoalveolar lavages [28]. However, given the high variability found in the BAL cellular profiles, the role of BAL is the diagnosis and management of AILT is limited [28].

Similarly to other etiologies of ARDS, the radiographic presentation is characterized by diffuse bilateral, interstitial infiltrates, confluent ground glass and airspace opacities and often thickened interlobular septa, originating a crazy paving pattern [18].

Consistent with the ARDS literature, reported mortality for the ARDS presentation of AIPT can reach 50% [24,31,33,39]. Unfortunately, the available literature is either dated, or limited to case reports.

Other, rarer radiographic presentations of AIPT include pleural effusions [40], nodular opacities, singular or multiple subpleural masses [41,42] and eosinophilic pneumonia [43].

Cases Series

Demographic, clinical and radiographic characteristics of the patients are shown in Table 1.

Case 1

A 68-year-old male with a medical history of cardiomyopathy secondary to coronary artery disease with a left ventricular ejection fraction (LVEF) of 25%, coronary artery bypass graft (CABG) and chronic atrial fibrillation and ventricular tachycardia, requiring multiple antiarrhythmic medications. Amiodarone therapy (200 mg daily) was administered for 2 years and it was ceased 2 weeks prior to presentation, due to amiodarone-induced liver toxicity observed on CT scan (slightly hyperdense liver).

The patient reported mild shortness of breath MRC dyspnea score of 1. On chest auscultation, there were inspiratory crackles on the left base. On PFTs, FVC was 82% of predicted, TLC 93%, and DLCO 48%. 6MWD was 484 meters (99% of predicted), with no desaturation.

HRCT showed mild, subpleural reticular interstitial changes with lower lobes predominance (Figure 1A). An HRCT done 2 years prior, when the patient was already on amiodarone, showed airspace opacities in the subpleural areas of the right lung.

Given the clinical stability and excellent exercise capacity, no specific treatment for AIPT was initiated, and the patient remained stable over a two-year follow-up period.

Case 2

A 78-year-old female with a history of interstitial lung abnormalities, which had been stable for the previous 4 years and never required any treatment, neurofibromatosis, mitral valve prolapse, and ductal carcinoma *in situ* of the breast, presented with progressive exertional dyspnea (MRC dyspnea score 4 on a scale of 0 to 5). Amiodarone (100 mg daily) was started for rhythm control for atrial fibrillation 10 months before this presentation.

The patient did not have significant environmental, professional or domestic exposures. and had no features of connective tissue disease.

Pulmonary function tests (PFTs) demonstrated a decline in forced vital capacity (FVC) from a baseline of 115% to 82%, of total lung capacity (TLC) from 83% to 73% and of DLCO from 62% to 50%. On the 6-minute walk test (6MWT), walking distance decreased from a baseline of 443 meters to 330 meters, and also with desaturation to 79% on room air.

HRCT showed diffuse, bilateral ground glass opacities, interlobular septal thickening, and developing peripheral airspace opacity (Figure 1B).

Amiodarone therapy was promptly discontinued, and the patient was initiated on prednisone 40 mg for 5 weeks along with trimethoprim-sulfamethoxazole prophylaxis.

Unfortunately, the patient soon developed significant adverse effects from the prednisone, necessitating the introduction of steroid-sparing agents. However, both mycophenolic acid and azathioprine failed to improve the patient's symptoms and physiology. Ultimately, maintenance therapy with a low dose of prednisone 5 mg resulted in progressive symptomatic improvement, stabilization of lung function, improvement of 6-minute walk distance (6MWD) and radiographic improvement over the 5-months period following the discontinuation of amiodarone.

Case 3

A 78-year-old male with a medical history of ischemic cardiomyopathy, diabetes, stroke, chronic kidney disease presented with increasing dyspnea and non-productive cough. He had been on amiodarone (200 mg daily) for 3 years to treat ventricular tachycardia. This was complicated by amiodarone-induced hypothyroidism. He had a history of multiple implantable cardioverter-defibrillator (ICD) shocks and was seen while admitted under the Cardiology service to address device malfunction and decompensated heart failure. He was found to be mildly hypoxic, with imaging suggestive of ILD. The chest CT scan showed reticular opacities, predominant in the right upper lobe, minimal ground-glass opacities, bronchiolectasis and focal honeycombing (Figure 1C).

PFTs demonstrated restrictive ventilatory defect with decreased diffusion capacity: FVC 57% pred, TLC 52%, DLCO 28%.

There was no occupational or environmental exposures of concern. AIPT was suspected and amiodarone tapered and eventually discontinued. Prednisone (40 mg for 5 weeks, then tapered down to 20 mg) was initiated, resulting in stabilization of the ILD. Prednisone was then further tapered and stopped completely within a few months. A repeat CT scan one year later showed stability of ILD.

Case 4

A 67 years old male with type II diabetes, moderate-severe chronic renal insufficiency hypertension, ischemic heart disease and sleep apnea presented with hypoxemic respiratory failure. Exertional dyspnea had started 3 months prior, and rapidly worsened in the previous 20 days. He had been on amiodarone therapy (200 mg) for 2 years for treatment of paroxysmal atrial fibrillation.

The chest CT scan demonstrated the presence of a reticular-nodular pattern, involving all lobes, with diffuse distribution (Figure 1D).

An echocardiogram revealed mild left ventricular dysfunction (ejection fraction 48%) with septal and apical akinesia, consistent with historic echocardiographic findings.

The patient's oxygen requirements progressively increased, with worsening of his clinical condition. Laboratory tests showed a slightly elevated pro-BNP, and furosemide was started, but this did not improve the hypoxia. Antibiotic therapy with piperacillin/tazobactam and linezolid

was initiated. Autoimmune markers were negative. A bronchoscopy could not be performed, due to the high oxygen requirements.

Given the concern over AIPT, amiodarone was discontinued and corticosteroid therapy started. Amiodarone-induced thyroid toxicity was also noted. With this, the patient's respiratory status gradually improved. The patient transitioned from high-flow nasal cannula to regular nasal cannula. Gradual improvement followed ad the patient was discharged home without oxygen needs.

Case 5

An 80 years old female, never smoker, who had been on amiodarone 100 mg for 5 years to treat chronic atrial fibrillation, presented with gradual onset of exertional dyspnea and productive cough, followed by the development of hypoxia. The HRCT showed confluent airspace opacities and, to a less degree, surrounding ground glass opacities (Figure 1E). Amiodarone was stopped and corticosteroid therapy started. Hypoxia resolved and corticosteroids were continued for 2 more months, until the complete resolution of opacites was obtained.

Case 6

An 81 years old male presented to ER of the local hospital with hypoxia. The patient had a history of ischemic heart disease with reduced ejection fraction and previous percutaneous coronary intervention (2 stents), chronic atrial fibrillation and chronic, right-sided, transudative pleural effusion. He had been on amiodarone 200 mg for 11 months. The patient had a recent history of “wax and weaning” pneumonia for the past 4 weeks, prevalently in the right lung, for which he received a 3 consecutive course of antibiotics, but without complete radiographic resolution. During this period, the patient developed a productive cough, weakness, intermittent fever and a 11 kilograms weight loss. Upon admission to hospital, the patient required 2 l/min of supplemental oxygen, administered with nasal prongs. On chest CT scan, the airspace opacites were more extensive and diffuse (Figure 1F). Given the lack of improvement after aggressive diuretic treatment and broad-spectrum i.v. antibiotics, he was transferred to General Medicine Unit of the regional tertiary centre. A new thoracentesis confirmed that the pleural effusion was transudative, sterile and with normal cytology. Differential cell count was prevalently neutrophilic. Given that the pleural effusion was first noted 9 months after staring amiodarone, and never before, it is not excluded that it was also a manifestation of amiodarone toxicity. A

bronchoscopy was also performed. All BAL cultures were negative. Differential cell count was slightly lymphocytic. Transbronchial biopsies showed chronic interstitial inflammation and a rare giant cell within the interstitium. Radiology review revealed that the chest x-rays have been abnormal for at least 8 months prior to presentation, with prevalently right-sided airspace opacities. AIPT was suspected and amiodarone was discontinued. After some hesitancy due to the cardiac underlying condition, prednisone treatment was eventually started. Unfortunately, soon after the procedures, clinical conditions started to rapidly deteriorate, with progressive worsening of the lung infiltrates and of the hypoxia, and the patient passed away 23 days after the initial admission.

Discussion

The case series presented and the review of the literature depicts AIPT as a broad spectrum of pulmonary disease that ranges from an isolated DLCO reduction without clinical implications to a life-threatening hypoxemic respiratory failure, consistent with ARDS. The interpretation of imaging findings plays a key role in ascertaining the severity of the pulmonary toxicity reaction. Specifically, the severity of the parenchymal involvement, as assessed on CT, may predict the severity of the clinical course. Cases of isolated DLCO reduction are characterized by minimal interstitial changes, without airspace component and without actual fibrosis. Such cases may go entirely unnoticed. If a DLCO reduction is detected in an asymptomatic patient, the clinician may obtain a HRCT to rule out early onset AILT. Alveolar-interstitial pneumonias cases with interstitial and/or airspace involvement, instead, are always clinically significant and require treatment. This is the most common clinical presentation of AIPT, with much more significant parenchymal involvement on CT, consisting of either a combination of interstitial thickening, ground glass and reticular opacites or, in organizing pneumonia cases, a prevalently airspace-consolidation pattern. Finally, severe cases of AIPT are rare, present with extensive and rapidly worsening airspace opacities, but are unfortunately life-threatening, meeting all the clinical criteria for ARDS.

In our series, case 1 represented a case of isolated DLCO reduction, sometimes called “amiodarone effect”, with minimal radiographic changes, and required no intervention. Cases 2 to 4 were cases of interstitial pneumonia with pattern suggestive of NSIP and were clinically significant, causing some degree of hypoxia and requiring treatment. Case 5 was of similar clinical severity, with pattern suggestive of organizing pneumonia as the main underlying

pattern. Case 6, unfortunately, was recognized late as AIPT and evolved to ARDS, eventually leading to patient's demise. The cases presented were of increasing clinical severity, and displayed a good correlation between the extent of the radiographic involvement and the significance of the clinical course.

The radiographic patterns of AIPT received limited attention in the literature. Many case series anecdotally described the CT findings, but did not define the specific patterns. The largest case series, published by Kang et al, did not find any case of usual interstitial pneumonia pattern (UIP) pattern with AIPT [7]. As mentioned in the introduction, the 3 main radiographic patterns of clinically significant cases of AIPT are represented by patterns suggestive of organizing pneumonia, NSIP and ARDS.

In AIPT-related organizing pneumonia, peripheral or peribronchial consolidations, typically patchy and non-segmental, are predominantly located in subpleural or peribronchial regions. These consolidations are often accompanied by adjacent ground-glass opacities, reflecting a mixed pattern of alveolar and interstitial involvement. The reversed halo sign, a central ground-glass opacity encircled by a denser rim of consolidation, and air bronchograms, air-filled bronchi visible within areas of consolidation, can also be observed [7,24,26].

In AIPT-related NSIP, diffuse or patchy ground-glass opacities, lacking the sharply defined consolidation typical of organizing pneumonia, are observed. Fine reticular opacities, representing interstitial thickening, are often seen in the lower lobes, and subpleural sparing is a characteristic feature. Traction bronchiectasis indicates fibrotic changes. This pattern typically presents symmetrically, affecting the lower lung fields [7,24,44].

In AIPT-related ARDS, as in other etiologies of ARDS, diffuse bilateral ground-glass opacities and consolidations are observed on CT. A classic feature of ARDS is the "crazy paving pattern", which consists of ground-glass opacities overlaid with thickened interlobular septa [37,45,46].

Given their underlying cardiac disease, patients with AILT may present also with cardiogenic pulmonary edema. The combined presence of bilateral, symmetric pleural effusions, cardionmegaly and interlobular septal thickening ("polygon" pattern) suggest the presence of pulmonary edema caused by left ventricular dysfunction, which should be correlated with clinical and echocardiographic findings.

An interesting aspect of amiodarone-induced toxicity is the occurrence of multi-organ involvement. The finding of high attenuation, due to iodine accumulation, in the liver, spleen and myocardium [47] are indicative of amiodarone-related lesions, but they do not necessarily

indicate toxicity [16]). In fact, the extent and the severity of hepatic attenuation observed on CT scan are not necessarily correlated with the total exposure to amiodarone over time [48]. Finally, amiodarone-associated liver injury, including fibrosis, usually occur independently or, much less frequently, concomitantly with pulmonary toxicity [49,50].

Conclusions

Amiodarone is an effective antiarrhythmic therapy that infrequently causes lung toxicity. As of other types of drug-induced lung toxicity, the diagnosis of AIPT remains a diagnosis of exclusion. The temporal association between amiodarone exposure and respiratory dysfunction remains crucial in establishing the diagnosis. Considering the observed correlation between radiographic involvement and severity of the clinical course, when new, diffuse, progressing patterns of interstitial lung disease and/or organizing pneumonia are observed, aggressive corticosteroid treatment and supportive therapies should be instituted without delay. Even limited exposure to low-dose amiodarone can cause significant AIPT, with hypoxia. Given the pharmacokinetics properties of amiodarone, AIPT can also occur months after the cessation of treatment.

As cardiogenic pulmonary edema and AIPT are frequently concomitant, the interpretation of the chest x-ray, even when compared to previous films, may be challenging. Considering the broad spectrum of radiographic presentations, when AIPT is suspected, a chest CT scan and expert radiology assessment should be obtained. The correlation of the CT pattern with lung function results and with the clinical presentation will provide guidance to the clinician in terms of amiodarone cessation, administration of supportive treatment and initiation of corticosteroid therapy.

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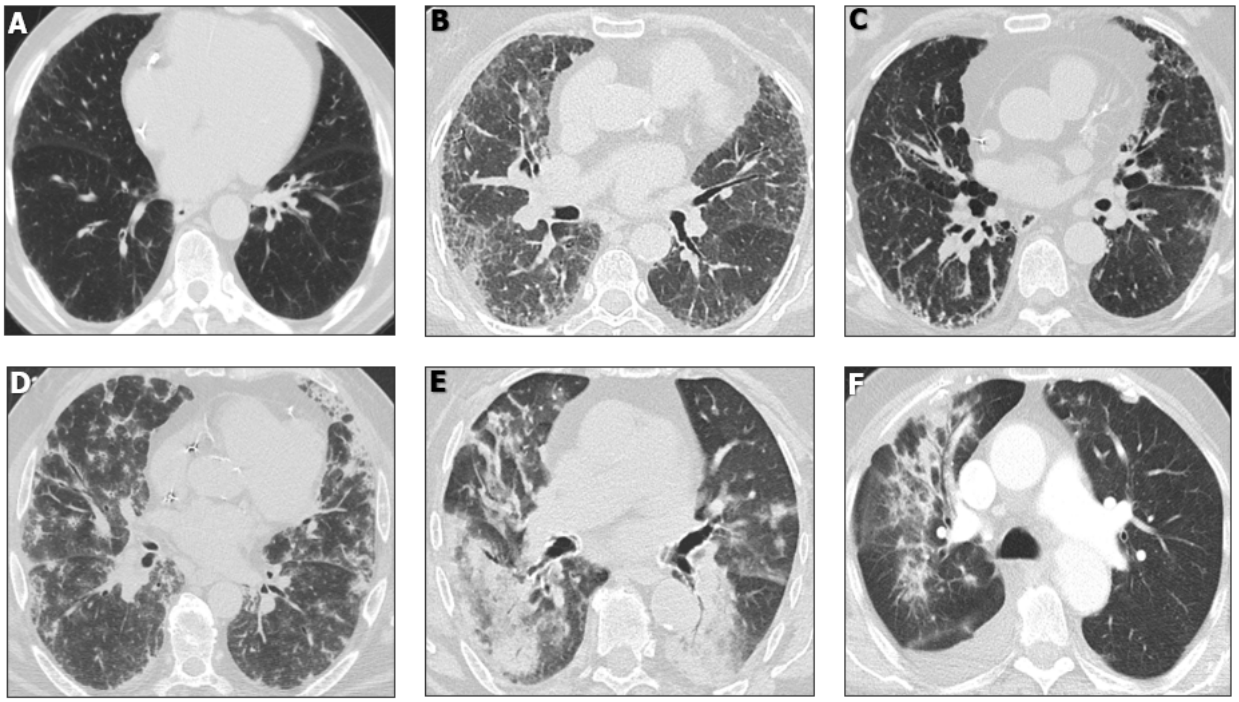

Figure 1. Representative cuts of the chest CT scans of each case presented, at the time of AIPT diagnosis. A) Case 1. Mild, reticular, and ground glass opacities and interlobular septal thickening with lower lobe predominance. B) Case 2. Diffuse, bilateral ground glass opacities, interlobular septal thickening and developing peripheral airspace opacity in the right lower lobe. C) Case 3. Reticular opacities, minimal ground-glass opacities, bronchioloectasis and focal honeycombing. D) Case 4. Reticular-nodular pattern, involving all lobes, with diffuse distribution, and ground glass opacities in the background. E) Case 5. Confluent airspace opacities and surrounding ground glass opacities with diffuse distribution, but worse in the lower lobes. F) Case 6. Developing airspace opacities prevalently in the right lung, surrounding ground glass opacities, interlobular septal thickening and ipsilateral pleural effusion.

Table 1. Demographic, clinical and radiographic characteristics of the patients included in the study.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	68	78	78	67	80	81
Sex	Male	Female	Male	Male	Female	Male
Amiodarone exposure	200 mg for 24 months	100 mg for 10 months	200 mg for 36 months	200 mg for 24 months	100 mg for 60 months	200 mg for 11 months
CT pattern	Mild, subpleural reticular opacities with lower lobes predominance	Diffuse, bilateral ground glass opacities, interlobular septal thickening, developing peripheral airspace opacity	Reticular opacities, predominant in the right upper lobe, minimal ground-glass opacities, bronchiolectasis, focal honeycombing	Reticular-nodular pattern, involving all lobes, with diffuse distribution	Confluent airspace opacities and, to a less degree, surrounding ground glass opacities	Extensive and diffuse airspace opacites
Treatment	None	Prednisone	Prednisone	Diuretics and prednisone	Prednisone	Diuretics and prednisone
Outcome	Alive and well	Stabilization	Stabilization	Resolution of hypoxia	Resolution of hypoxia	Passed away