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CASE REPORT

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Acute breathlessness with frank hemoptysis following catheter ablation for atrial fibrillation, a cause not so obvious

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Key Clinical Message

All clinicians prescribing amiodarone require knowledge of the challenging diagnosis and management of amiodarone-induced pulmonary toxicity (APT), which is potentially fatal. APT should be considered early in all patients presenting with new respiratory symptoms and concurrent amiodarone therapy. Drug cessation and corticosteroid therapy can be highly effective once recognized.

1 | INTRODUCTION

Amiodarone is an effective anti-arrhythmic drug, safe to use in ischemic heart disease and heart failure, with a broad range of indications, including the treatment of atrial fibrillation (AF). Due to its anti-arrhythmic efficacy, it is one of the most common anti-arrhythmic drug prescriptions in England[1] despite the well-recognized multitude of side effects, which are often dose dependent.[2] A meta-analysis has demonstrated that the use of low-dose amiodarone (<400 mg/d) is still associated with a significant risk of thyroid, neurologic, skin, ocular, and bradycardic adverse events.[2] There is also a trend toward increased risk of pulmonary toxicity with even low-dose treatment. Amiodarone-induced pulmonary toxicity (APT) has the greatest potential for fatality,[3] with risk typically rising in a cumulative dose-dependent nature. The presentation of APT is heterogenous,[4-7] including parenchymal or pleural changes. The varied nature of APT and nonspecific symptoms makes diagnosis challenging particularly in patients with multiple comorbidities and cardiorespiratory disease. This report follows the CARE guidelines for clinical case reporting.[8]

2 | CASE PRESENTATION

A 71-year-old male was referred for elective repeat catheter ablation for persistent symptomatic AF. AF was diagnosed in 2008 with three subsequent unsuccessful cardioversions. The first catheter ablation with pulmonary vein isolation was performed using radiofrequency in June 2015. Sinus rhythm was maintained for 9 months, with good symptom resolution. The patient reported symptoms of shortness of breath with reduced exercise capacity when in atrial fibrillation. There were no signs of heart failure, and he was in New York Heart Association functional class II. Echocardiography demonstrated a structurally normal heart with good left ventricular (LV) systolic function and a left atrial diameter of 3.8 cm (normal range 3.0-4.0 cm).

Past medical history included hypercholesterolemia. Medications included: warfarin, bisoprolol 5 mg once daily, and atorvastatin 10 mg once daily. Amiodarone had been used previously for 6 months during 2015 around his first AF ablation. There were no known drug allergies.

Repeat catheter ablation for AF was performed in July 2017 under general anesthetic on uninterrupted warfarin with a therapeutic INR. Oxygen therapy was delivered during anesthesia with a fraction of inspired oxygen of 0.25. A trans-esophageal echocardiogram was performed to exclude left atrial thrombus and guide trans-septal access. The procedure duration was 2 hours 30 minutes with an ablation strategy including re-isolation of two pulmonary veins, additional ablation of areas of complex fractionated electrograms and empirical linear roof and mitral lines. Amiodarone was

commenced at 200 mg three times daily with the first dose administered 2 hours following the procedure, to be reduced to 200 mg daily over three weeks.

Overnight the patient reported coughing, chest pain and haemoptysis with clots. Initial observations were within normal range, and physical examination was unremarkable except for blood-stained sputum. Blood results demonstrated normal biochemistry including normal urea, creatinine, and electrolytes, C-reactive protein (CRP) 15 mg/L. Hemoglobin 120 g/L (159 g/L preprocedure), platelets 159, and white blood cells (WBC) 11.2×10^9/L, INR 1.8. Initially, the differential diagnoses included bacterial or viral pneumonia, LV failure with pulmonary edema, pulmonary vein trauma/stenosis, and pulmonary embolus with hemorrhage exacerbated by therapeutic anticoagulation.

Chest radiograph (Figure 1) and high-resolution CT chest with contrast were performed (Figure 2), which demonstrated extensive patchy nodular and confluent ground glass opacification in the left lower lobe, lingula, and the posterior aspect of the right lower lobe. The main pulmonary veins were patent and there were no signs of esophageal injury or pneumomediastinum. Appearances were in keeping with bilateral pulmonary hemorrhage of unclear cause. An echocardiogram revealed good LV systolic function and no significant valvular abnormalities.

On day 2, the patient remained symptomatic with frank haemoptysis, pleuritic chest pain, and hypoxia and had developed fevers. Blood and sputum cultures (including acid-fast bacillus) were sent prior to commencing empirical intravenous co-amoxiclav with continuation of warfarin and a trial of furosemide. A respiratory physician opinion was sought and recommended that pulmonary vein trauma was the likely cause; however, serial chest radiography demonstrated worsening bilateral changes. A serum autoimmune screen (ANCA and anti-GBM) was also requested which was normal. Day 4 postablation, the patient remained symptomatic with frank haemoptysis and hypoxia requiring 3 L/min of oxygen. Physical examination revealed bilateral fine inspiratory crepitations in mid/lower zones with no signs of decompensated heart failure. The CRP peaked at 143 on day 5 postablation, WBC, and eosinophil counts remained normal on subsequent daily bloods. Neither blood nor sputum cultures grew any significant organisms.

By day 5 postablation, pulmonary vein trauma and infection were considered unlikely, a third consultant cardiologist opinion suggested the diagnosis of acute APT and amiodarone was stopped. Corticosteroid therapy was commenced with 30 mg of oral prednisolone. Within 24 hours oxygen saturations had normalized and the symptoms had significantly improved with no additional haemoptysis. The patient completed 7 days of oral co-amoxiclav and prednisolone, following which he was discharged home. Subsequent outpatient follow-up at 3 and 6 months revealed no recurrence of symptoms and complete resolution of radiographic findings; he has remained in sinus rhythm and symptomatically well at over 6 months postablation.

3 | DISCUSSION

This case of APT highlights the potential for acute presentations occurring within 24 hours of amiodarone administration in patients with previous uneventful exposure. It also highlights the diagnostic challenges following cardiac ablation due to the range of differential diagnoses including pulmonary vein stenosis, a rare but serious complication which occurs in approximately 0.3%-0.8%.[9,10] What is unusual in this case is the rapidity of onset of pulmonary toxicity, within

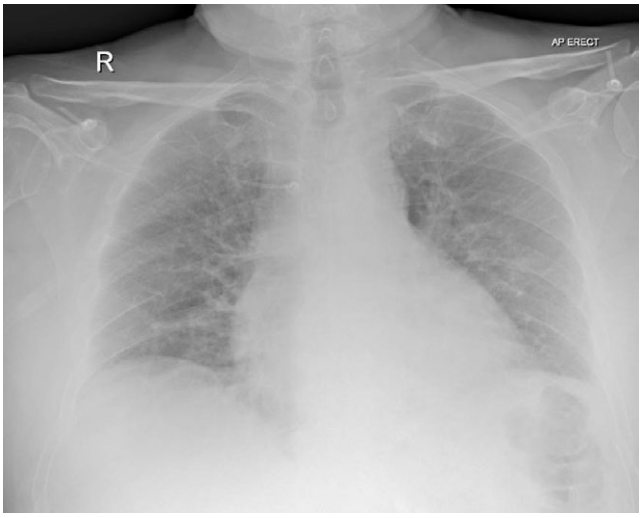

FIGURE 1 Chest radiograph showing bilateral hilar and lower zone consolidation and small pleural effusions

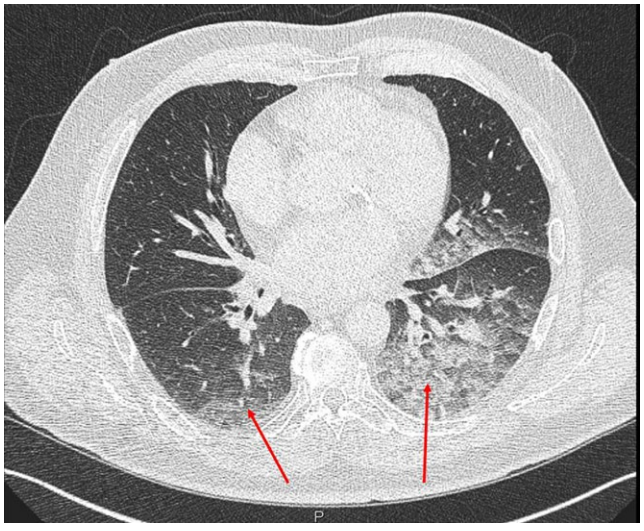

FIGURE 2 CT chest showing bilateral pulmonary hemorrhage (arrows point to patchy nodular and confluent ground glass opacification consistent with pulmonary hemorrhage)

1-2 doses. This is particularly relevant in cardiac centers where amiodarone is used on a broad range of patients including those with risk factors for APT. Several experienced physicians, 3 senior cardiologists, and a respiratory physician assessed the patient over 5 days before the diagnosis of acute APT was considered. This reiterates the importance of awareness of APT to enable prompt diagnosis and correct management.

Several forms of APT exist including interstitial pneumonitis, exudative pleural effusions, organizing pneumonia, bronchiolitis obliterans, acute respiratory distress syndrome, and pulmonary masses. The clinical syndrome can be nonspecific, and a high index of clinical suspicion is required to diagnose APT. Haemoptysis is previously described as a serious but rare presentation of APT.[11]

An accurate estimate of risk of amiodarone-induced pulmonary toxicity has not been established, although studies have reported a range of 5%-13%[12] with an excess risk of 1% per year.[13] Several potential risk factors have been suggested including: high cumulative dose of 101-150 g,[14] duration of therapy more than 2 months, daily dose >400 mg/d,[15] advanced patient age,[16,17] and preexisting lung disease.[18] ARDS presentations can occur in the setting of cardiothoracic surgery.[19]

The timescale of presentation is variable and often under recognized. Pulmonary hemorrhage with haemoptysis is previously described in the literature with acute onset after many days of administration; however, this case demonstrates the potential for hyperacute onset within 24 hours of drug initiation, not been previously described. The mechanism underlying APT is likely to be multifactorial, two likely hypotheses are recognized. The first involves direct toxic injury to the lung from the drug or its metabolites; the second is an immunological reaction to the drug.[18,19]

APT has a range of clinical signs and symptoms; manifestations include cough, dyspnoea, fever, weight loss, chest pain, bilateral lung infiltrates, and haemoptysis. In this case, the differential diagnoses included pulmonary vascular injury resulting from catheter ablation, pulmonary embolus and/or infarction, bacterial pneumonia, LV dysfunction with acute pulmonary edema, eosinophilic pneumonia, and adverse drug reactions.

An additional challenge with this case included balancing the risk of major pulmonary hemorrhage with uninterrupted anticoagulation, against the risk of thrombotic stroke following left atrial catheter ablation. What is also unusual about this case was that the patient had previously taken amiodarone for several months without any reaction, and such profound acute pulmonary pneumonitis can occur almost immediately on drug administration.

Discontinuation of amiodarone may be sufficient to halt and reverse mild forms of APT; however, corticosteroids can be used to accelerate resolution of the acute inflammatory effect of the drug. Due to amiodarone's long half-life and lipophilic properties, short courses of steroids may not be sufficient and some recommendations include up to 6 months of steroid treatment. There are no controlled studies available nor are there likely to be any in the future to guide management. A sufficient initial dose is typically prednisolone 0.75-1.0 mg/kg including maintenance until clear clinical and radiographic resolution, followed by slow weaning of the drug over days.[20] The risk benefit of chronic corticosteroid therapy must be balanced by the physician.

4 | CONCLUSION

This case demonstrates a rare but recognized APT reaction presenting with hypoxia and pulmonary hemorrhage on a timescale not previously described. Previous exposure does not rule out future reactions, which can be almost immediate causing fulminant hemorrhage and haemoptysis. It also highlights the breadth of potential scenarios for APT presentation, in this example with rapid onset after elective catheter ablation, creating diagnostic uncertainty and treatment delay. Finally, it demonstrates the importance of clinical acumen in the context of modern medicine where high-resolution cross-sectional imaging may not clarify the etiology of acute presentations.

The patient's perspective was one of prolonged hospital admission with a period of illness and uncertainty out of proportion to their expectations for an elective procedure. This episode of APT caused great anxiety for the patient and his family. Their experience was markedly different to the majority of patients undergoing AF catheter ablation who are typically discharged within 24 hours. Establishing a precise diagnosis and clear communication was fundamental to their coping with this period of illness.

CONFLICT OF INTEREST

None declared.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

AUTHOR CONTRIBUTIONS

PHW: conceived and wrote the article; AMCC: reviewed and edited the article.

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