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CASE REPORT

Amiodarone toxicity: recurrence of interstitial pneumonitis after withdrawal of the drug

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Amiodarone toxicity: recurrence of interstitial pneumonitis after withdrawal of the drug. O. Parra, J. Ruiz, I. Ojanguren, J.J. Navas, J. Morera.
ABSTRACT: Amiodarone hydrochloride, an iodinated benzofuran derivative, is effective for treatment of supraventricular and ventricular arrhythmias. Pulmonary fibrosis has been reported after treatment with this drug . We present a patient with amiodarone pulmonary toxicity, who initially responded to corticosteroid therapy, but who developed a clinical relapse two months after withdrawal of the drug.
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Amiodarone hydrochoride, an iodinated benzofuran derivative, is an effective drug in the treatment of supraventricular and ventricular arrhythmias [1]. Several toxic effects of the drug were already known [2] but in 1980 pulmonary toxicity was initially suggested by ROTMENSCH *et al.* [3] and later described by HERGER *et al.* [1]. The diagnosis is quite often very difficult because there are no specific signs of toxicity [4]. It must be an exclusion diagnosis based on amiodarone taking antecedents, with a good response by discontinuing the drug and steroid addition. As far as we know, only a few cases of recurrence of pulmonary symptoms have been reported [5].

We present a patient with amiodarone pulmonary toxicity who initially responded to corticosteroid therapy but who developed a clinical relapse after two months of treatment withdrawal.

Case Report

A 60 yr old, 12 packs per year, male smoker was treated with amiodarone for recurrent supraventricular and ventricular arrhythmias secondary to ischaemic cardiopathy.

Amiodarone was initiated at a dose of 400 mg per day, 5 days a week. After 14 months of amiodarone therapy, with a cumulative dose of 120 g, he presented non-productive cough, low grade fever and progressive dyspnoea on exertion. On admission he was febrile, dry basilar rales were noted bilaterally and there were no signs of congestive heart failure. Chest X-ray showed bilateral and diffuse interstitial infiltrates with some areas of confluence (fig. 1). Laboratory data were normal. Room air arterial blood gas determination showed: arterial oxygen tension (Pao_2) 4.5 kPa (34 mmHg) and arterial carbon dioxide tension ($Paco_2$) 4.8 kPa (36 mmHg). A haemodynamic study with a Swan-Ganz catheter showed a pulmonary capillary wedge of 10 mmHg, ruling out the possibility of heart failure. Lung function tests revealed a restrictive disease forced vital capacity (FVC) 62%, forced expiratory volume in one second (FEV_1) 69%, FEV_1/FVC 81% of predicted) with a markedly impaired carbon monoxide diffusion capacity (TLCO 20% of predicted). A gallium scan showed increased uptake throughout both lung fields.

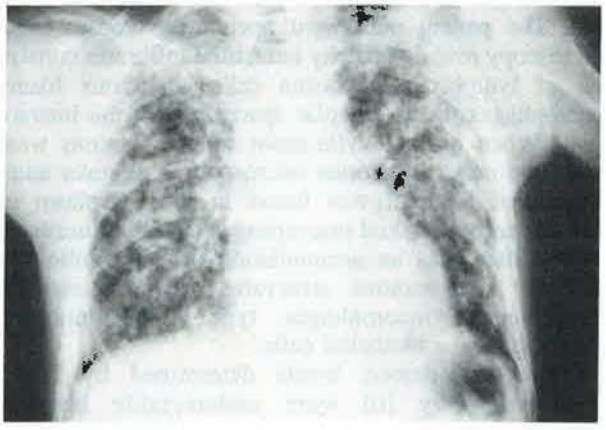

Fig. 1. – Chest X-ray showing diffuse interstitial infiltrates at first admission.

Amiodarone pulmonary toxicity was suspected, and this medication was discontinued, starting treatment with 1 $mg \cdot kg^{-1}$ per day of 6 methyl-prednisolone. After 15 days of steroid therapy the patient improved dramatically and oxygen could be discontinued. After one month of treatment he was discharged with 1 $mg \cdot kg^{-1}$ of steroids on alternate days. In later controls chest X-ray and function tests improved progressively, achieving normal patterns at 3 and 4 months, respectively. At this point steroids were gradually decreased, and after 4 months they were discontinued.

Two months later the patient relapsed, with fever, cough, bilateral rales on exploration and bilateral interstitial infiltrates in the chest X-ray (fig. 2). Laboratory findings were normal. Pulmonary function tests were in the normal range except for TLCO, which was 17% of the predicted value. Gallium scan showed similar increased uptake and a haemodynamic study again dismissed cardiac failure.

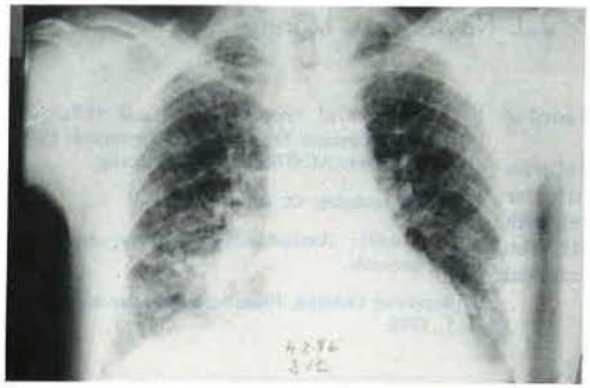

Fig. 2. – Chest X-ray showing diffuse interstitial infiltrates at second admission.

We performed a bronchoalveolar lavage with 104 cells·mm^{-3}: 61% lymphocytes, 35% macrophages, 3% eosinophils), (normal values in our department: 80–90% macrophages, 5–15% lymphocytes, 5% granulocytes, 1% basophils or eosinophils). Transbronchial biopsy showed interstitial pneumonitis with no presence of any of the characteristic findings of amiodarone tissue impregnation. The patient underwent open lung biopsy. Light microscopy revealed patchy interstitial infiltrates consisting of lymphocytes, plasma cells, numerous foamy macrophages in the alveolar spaces and in the interstitium. When haematoxylin-eosin stained sections were examined under ultraviolet microscopy a granular autofluorescent material was found in the cytoplasm of alveolar and interstitial macrophages (fig. 3). Ultrastructurally there was an accumulation of osmophilic and lamellar membranous structures within distended lysosomes of macrophages, type II pneumocytes, interstitial and endothelial cells.

Serum amiodarone levels determined by liquid chromatography [6] were undetectable but the biopsy demonstrated the persistence of amiodarone (2.5 mg·g^{-1} of pulmonary tissue) and desethylamiodarone (9 mg·g^{-1} of pulmonary tissue) in lung parenchyma.

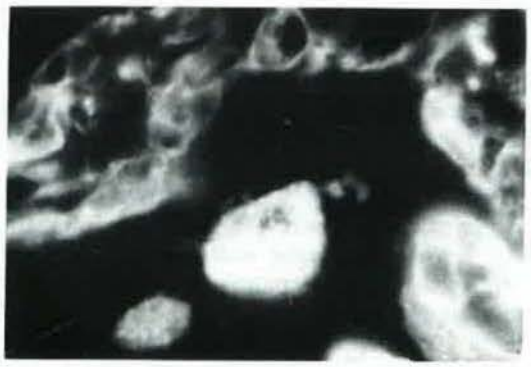

Fig. 3. – Autofluorescence from granular cytoplasmatic formations in an alveolar macrophage.

The symptoms again resolved with the administration of oral steroids. Chest X-ray and function tests became normal in the fifth month. Corticosteroid therapy was continued for 6 months. After three years the patient remained asymptomatic with normal chest X-ray and function tests, but died because of an acute myocardial infarction. Table 1 shows the pulmonary function data.

Table 1. – Pulmonary function tests

Date	FVC % pred	FEV_1 % pred	FEV_1/FVC %	TLCO % pred
5/5/85	69	73	80	20
3/9/85	100	96	81	85
6/2/86	100	96	80	17
16/7/86	90	95	80	102

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; TLCO: transfer factor of lungs for carbon monoxide.

Discussion

The initial presentation and evolution of this case was quite similar to previously reported cases of amiodarone pulmonary toxicity. This is the reason why we excluded other etiologies; we suspected this diagnosis, and without histological confirmation proceeded to discontinue amiodarone and start corticosteroid therapy, obtaining good results. We could not determine serum amiodarone levels initially but we did when the patient relapsed. Although pharmacokinetic studies of amiodarone have reported an elimination half-life of 13–60 days [7] there is little information correlating serum amiodarone levels and amiodarone-related toxicity. Besides, the relatively low serum amiodarone levels may not adequately reflect the tissue levels of the drug, which have been reported to be significantly higher than those found in serum [8], as we were able to demonstrate by liquid chromatography [6]. In our case we could see the characteristic signs, previously described for impregnation of amiodarone [9], after 6 months of drug withdrawal. This fact, as well as the detection of amiodarone in lung tissue, allowed us to ascribe the recurrence of symptoms in our patient to amiodarone.

We have to point out that in relapse only TLCO was reduced, FVC and FEV_1 being in the normal range; this fact probably relates with an earlier stage of amiodarone pulmonary damage.

An important histological finding is the presence of autofluorescent granular material in the cytoplasm of alveolar and interstitial macrophages, corresponding to complex lipid intralysosomal storage secondary to an interaction in phospholipid catabolism. Ultraviolet microscopy, although not specific [10], could thus be a useful routine technique in the diagnostic approach in addition to ultrastructural study even when available material is scarce.

We wish to remark on the longest half-life of amiodarone we have ever known, the peculiarity of its autofluorescence and the possibility of recurrence and the necessity of reintroducing steroids with such a good response.

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Toxicité de l'amiodarone: rechute d'une pneumonie interstitielle après retrait de la drogue. O. Parra, J. Ruiz, I. Ojanguren, J.J. Navas, J. Morera.

RÉSUMÉ: L'hydrochloride d'amiodarone, un dérivé iodé du benzofurane, est efficace pour le traitement des arythmies supraventriculaires et ventriculaires. L'on a rapporté des fibroses pulmonaires après traitement au moyen de ce médicament. Nous présentons une observation d'un patient atteint d'une toxicité du à l'amiodarone, qui a répondu initialement à la corticothérapie, mais qui a rechuté cliniquement deux mois après arrêt de ce traitement.

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