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Case report

Rapid onset of amiodarone induced pulmonary toxicity after lung lobe resection – A case report and review of recent literature

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HIGHLIGHTS

- Amiodarone-induced pulmonary toxicity (APT) can develop after low dose and short term amiodarone therapy.
- The early generation of APT is supported by thoracic surgery.
- APT can cause severe adult respiratory distress syndrome, leading to respiratory failure.
- Glucocorticoid therapy ameliorates APT symptoms and can restore respiratory failure in early state.

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ABSTRACT

Amiodarone-induced pulmonary toxicity (APT) is a severe side effect that can lead to lung fibrosis or fatal respiratory failure. Usually APT occurs during long term therapy after administration of prolonged loading doses or high cumulative doses. We present the case of a 58 year old woman who underwent thoracic surgery with lobe resection. She developed atrial fibrillation with hemodynamic-instability on the first post-operative day. We initiated amiodarone therapy and four days later she developed respiratory failure. The pulmonary function further deteriorated showing signs of an acute respiratory distress syndrome (ARDS). We therefore started mechanical ventilation, but still the gas exchange did not improve. A computer tomography-(CT)-scan presented bilateral interstitial and alveolar infiltrations. The patient also presented with leukocytosis, elevated C-reactive protein (CRP) levels however without elevated procalcitonin (PCT) concentrations. In the tracheal secretion we only harvested foam cells, but got no evidence for pathogens causing pneumonia. We immediately started glucocorticoid therapy with prednisolone 50 mg/d for five days. Almost instantaneously the gas exchange ameliorated. We were able to wean the patient from the respirator within five days. Pulmonary infiltrations were nearly vanished in a CT-scan few days later and completely disappeared in follow up examinations. This case demonstrates a per-acute onset of APT caused by a low loading dose in association with thoracic surgery. The initiation of glucocorticoid therapy in parallel to amiodarone withdrawal led to full recovery of the patient. One should consider APT when signs of pulmonary failure occur during brief periods of amiodarone therapy especially after thoracic surgery.

1. Introduction

Amiodarone is frequently used to treat effectively a broad variety of arrhythmias including atrial fibrillation. However it has a wide range of side effects among these APT occurs in approximately 2–10% of treated patients and it is the most severe side effect due to its association to amiodarone induced death [1]. Usually APT correlates with high cumulative doses that have been administered over months to years and with high daily doses above 400 mg [2]. The earliest appearance of APT has been reported to occur within few weeks after initiation of amiodarone treatment. The mechanisms underlying APT are rather complex and are not fully understood. It is assumed that amiodarone has either a direct toxic effect

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onto lung cells or via an indirect immunological pathway [3,4]. Both processes are supported by the fact that amiodarone and its metabolite desathylamiodarone accumulate in the lung where they reach concentrations that exceed serum levels by 100–500 times [5]. The cell injury induces a persistent inflammation causing a chronic pneumonitis eventually leading to lung fibrosis [6]. Main clinical diagnostic features are newly occurring dyspnea and decreased carbon monoxide diffusion capacity [7]. In conventional X-ray images APT displays mainly the pattern of regional to diffuse alveolar or interstitial opacities and can also present as a mixture of both [8,9]. However radiologic patterns can exist without clinical symptoms. So far we do not know any report about acute pulmonary toxicity that develops within few days after initiation of a low-dose amiodarone therapy. The following case report follows the SCARE criteria for surgical case reports [10].

2. Presentation of case

A 58 year old female patient underwent a right upper lobe resection because of an adenocarcinoma. Her medical history reported of preexisting chronic obstructive pulmonary disease, smoking, arterial hypertension, paroxysmal atrial fibrillation and diabetes mellitus type II. The lobe resection was performed via a thoracotomy under general anesthesia. The blood loss during this surgery was estimated at 800 ml, the patient received no transfusion. Two chest drains were inserted in “Bülau position” with negative pressure adjusted at 15 mmHg. Following the surgical procedure she was extubated and carried to the intensive care unit (ICU) breathing spontaneously. On the first postoperative day she developed atrial fibrillation with hemodynamic instability. According to the guidelines a biphasic cardioversion was applied three times (120 J each) without success. Heart frequency control was achieved with digitonin and metoprolol. In parallel we started oral amiodarone therapy with a loading dose of 3 times 200 mg/d. The maintenance dose of 200 mg/d was planned for further three months. Five days after starting the amiodarone therapy the patient developed dyspnea under light physical stress. A subsequent diuretic treatment did not improve the clinical aspect. Soon she developed an acute respiratory failure accompanied with leukocytosis of 32/nl but without fever. In several bronchoscopic lavages (BAL) we harvested specimen for microbiologic diagnostic. But we gained no evidence for an infectious pneumonia, however we started an empirical antibiotic therapy using piperacillin/tazobactam. In a subsequent CT-scan we detected diffuse bilateral opal consolidations (Fig. 1), pleural effusion with atelectasis of the middle lobe and enlarged pulmonary lymph nodes. A pulmonary arterial embolism was excluded. The respiratory situation further deteriorated showing the signs of a severe ARDS so we started invasive pressure controlled ventilation (F_iO_2: 0.9, PEEP: 14 cm H_2O, PaO_2/F_iO_2: 89). In repeated bronchoscopies we found clear mucus and physiological mucosa; in a further BAL we only harvested foam cells. A transthoracic echocardiography diagnosed normal global ventricular function. Using the pulse contour cardiac output technology we estimated slightly enhanced extravascular lung water index of 11.9 ml/kg. Histo-pathologic investigation of the excised right upper lobe obtained evidence of a adenocarcinoma with low grade differentiation. This pathological investigation provided no signs of any infection or other inflammatory or rheumatic process. Since we had no evidence for an infection we suspected an APT, only CRP levels were increased while PCT serum levels were unaltered (Table 1). We immediately stopped the amiodarone therapy and started prednisolone therapy with 50 mg/d. Several hours after the first prednisolone dose was administered the respiratory situation improved and we weaned the patient from the respirator. She was extubated three days later, still requiring non-invasive ventilation. She was discharged from the ICU to a low care ward two days later. Additionally the radiological aspect improved as demonstrated in a further CT-scan performed at the day she left the ICU (Fig. 1). The prednisolone therapy was maintained and slowly tapered. The patient fully recovered without any sign of recurrent symptoms after complete withdrawal of the glucocorticoid therapy. The Patient was routinely re-evaluated during the follow-up care period of two years. She still presents in a good condition with no further restrictions in her daily life. Consecutive CT-scans demonstrated no lung infiltrations or fibrotic remodelling one year after the APT incidence (Fig. 1c). Also in conventional thoracic radiograph taken two years later we found no structural residues of the APT (Fig. 1d).

3. Discussion

APT has initially been reported with varying incidences reaching 61% of treated patients [11]. Albeit in recent studies the incidence of APT ranges between 1.6% and 2.9%. These reduced APT incidences are nowadays achieved by using lower loading doses over brief periods followed by low maintenance doses [7,12].

However, APT may still occur after several months of amiodarone treatment and can also remain undetected or underestimated especially in intensive care patients [3,12,13]. The present case shows an unusual early development of APT. So far it has been reported, that APT follows after high dose amiodarone application for more than a week [14]. Thus we observed severe respiratory failure following five days after initiation of a low dose amiodarone therapy. So far this seems to be uncommon, in the current literature the period until respiration is being impaired is more prolonged ranging up to several months [15–17]. In few case reports APT became apparent only after the application of high cumulative amiodarone doses above 12.5 g which often lead to fatal outcome yet that is in contrast to this case [18–20]. Fatal outcomes may also occur long after the initiation of amiodarone therapy and too independently from the cumulative dose after the therapy had been finished. Overall mortality rates of APT range between 1 and 33% depending on the respiratory situation [2,19]. Further, thoracic surgery promotes the onset of APT, this observation is supported by the assumption that inflammatory processes are responsible for the generation of APT. The latter predominantly causes fatal outcome [14,21,22]. But there exists a high inter-individual diversity of amiodarone susceptibility ranging from early toxicity already induced after short term treatment <14 d to cumulative doses <10 g accompanied with low serum levels [19,23]. It has also been reported that low maintenance doses <305 mg/d do not prevent APT. According to the current data it is recommended to apply 200 mg/d as a maintenance dose to keep the probability for APT as low as possible [19].

Pivotal for APT generation is the amiodarone accumulation and its major metabolite desethylamiodarone in the lung where both reach concentrations of 100–500 fold compared to serum levels [5]. These high pulmonary concentrations also exceed concentrations in the heart, the classical amiodarone target. Further, amiodarone is compartimentalized mainly in pneumocytes type II. This accumulation accompanied with low tissue clearance rates further the theory of a direct toxicity [2,14]. However immunologic processes may also be relevant for the induction of long term lung damage or fibrosis [24]. The findings of the present case support an immunologic process in the generation of APT. We observed high serum concentrations of CRP and leukocytes but unaltered PCT levels and several sterile BAL probes. In the lung lobe that was excised before initiating the amiodarone therapy we found no evidence of inflammation or fibrosis, indicating that amiodarone was the sole inducer of the inflammation. Typical for APT seems to be