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NITROFURANTOIN-INDUCED LUNG DISEASE WITH FATAL OUTCOME: A CASE REPORT

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Abstract: An 81 year old patient was referred to our ECMO-center (extracorporeal membrane oxygenation) with acute respiratory distress syndrome after treatment with Nitrofurantoin for eight days. After ruling out other causes the diagnose "nitrofurantoin associated lung injury" was established and confirmed by CT-findings. Despite differentiated therapy and ECMO, clinically the patient passed away from finally occurred liver failure. Autopsy and histological examinations revealed extensive fibrosing and inflammatory processes in the lung tissue in the sense of drug-induced lung damage as well as signs of acute liver failure in the context of pre-final formation.

Keywords: adverse drug reaction, nitrofurantoin, lung disease, histology.

INTRODUCTION

Drug-induced lung disease is a rare and serious complication of several medication including antimicrobial therapy, nonsteroidal anti-inflammatory drug (NSAID's), immune suppressant and others. The histopathological manifestations are protean but often stereotypical. These reactions include diffuse alveolar damage, nonspecific interstitial pneumonia, eosinophilic Pneumonia [1]. Nitrofurantoin, which is commonly used for urinary tract infection (UTI), has potential adverse effect like pulmonary toxicity hepatitis cholestasis, peripheral neuropathy and aplastic anemia [1,2]. We report a case of an uncommon, but serious toxicity of nitrofurantoin with fatal outcome.

CASE REPORT

Medical history

An 81 year-old female patient with acute respiratory distress syndrome (ARDS) was presented to our ECMO-center (extracorporeal membrane oxygenation) with deteriorating respiratory function although using ventilatory-support with endotracheal tube and prone position. Her past medical history shows arterial hypertension, diabetes mellitus type 2 and hyperlipidemia. The initial work up was unspecific; it showed elevated inflammatory markers like White Blood Cells (WBC's), C-Reactive Protein (CRP) and prolactin. Initial X-ray showed bilateral reticular opacities and some atelectasis. The arterial blood gas showed a PO_2 below 100 mmHg with 100 % FiO_2 and pCO_2 was above 90mmHg. The patient was stabilized with venovenous extracorporeal membrane oxygenation therapy and transferred to our ECMO-center. We started broad-spectrum antibiotic therapy directly with Meropenem and Teicoplanin. The lab results and respiratory panel including blood and sputum cultures were negative. Thoracic CT was performed, which showed extensive bilaterally infiltrates, consolidation and a ground-glass appearance (Fig. 1). Because of lack of infectious agents and unknown cause for the imaging findings and the underlying symptoms, an autoimmune work up was performed, which was also negative. Consequently, a substance or drug pulmonary toxicity was assumed. Therefore, we took a detailed medical history. According to her family physician, the patient complained of dysuria over ten days and was taking NITROFURANTOIN over the last week. Earlier use of the drug could not be determined. According to the family, the patient had no previous lung disease or smoking history. A bronchoalveolar lavage was

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performed, which demonstrated eosinophilia. We commenced the patient on high dose cortisone therapy but the lung function did not show any improvement. After three weeks of supportive ECMO therapy, the patient died from finally occurred acute liver failure.

Autopsy findings

Autopsy revealed abnormal findings in the lungs and liver. Purely macroscopically, lung tissue of fleshy consistency with partially solidified, partially brittle areas was shown. The liver tissue presented itself in places with lightened areas in the sense of fine and coarse spots of liver tissue necroses.

Histological examinations showed extensive fibrosing and destructive inflammatory reactions in the lungs, which could be interpreted as a progressive process of inflammation and scarring (Fig. 2). The histopathological findings were consistent with nitrofurantoin induced lung fibrosis. Additionally, focal liver cell necroses with accompanying fresh inflammatory reaction were found, which were assessed as an expression of pre-final damage respectively acute liver failure.

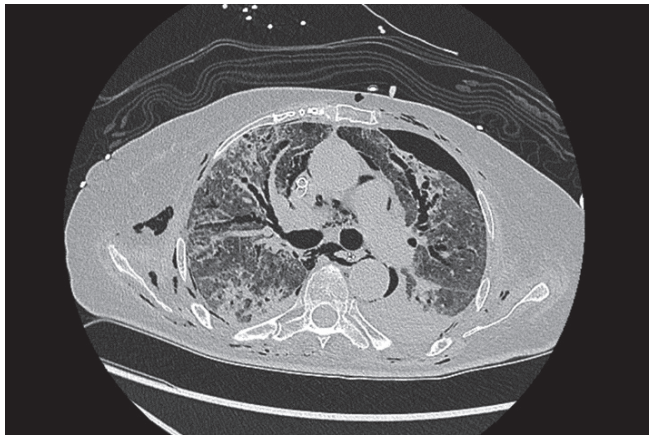

Figure 1. CT scan after four weeks on ECMO showing extensive bilaterally infiltrates, consolidation and a ground-glass appearance.

DISCUSSION

According to German national guidelines, Nitrofurantoin is a commonly used antibiotic in UTI [3]. Virtually, Nitrofurantoin is a prodrug which is activated by bacterial enzymes. The active compound exerts its bacteriostatic and bactericidal effects by inhibiting various enzymes and damaging bacterial DNA. Fisk described the first report of acute nitrofurantoin induced lung disease in 1957 [4].

Two forms of reactions are reported in the literature; acute and chronic side effects [5,6]. The acute form is more prevalent and usually occurs three to eight days after starting treatment [7]. The patients typically present with respiratory symptoms like cough, shortness of breath, chest pain and tachypnea. General features like fever, arthralgia and rash may also be present. In the chronic form liver damage with chronic hepatitis and focal or centrilobular necrosis as well as lung damage with interstitial pneumonitis, organizing pneumonia and pulmonary fibrosis have been described amongst other things [8-10]. These can usually arise after months or years, especially after long-term nitrofurantoin use [8,9]. In the patient information leaflet for nitrofurantoin, an increase in the frequency and severity of such reactions is related to the longer duration of the medication. These cases were observed above all, when the drug was taken for more than six months [11]. The fact that in the histological examinations, chronic lung damage in the

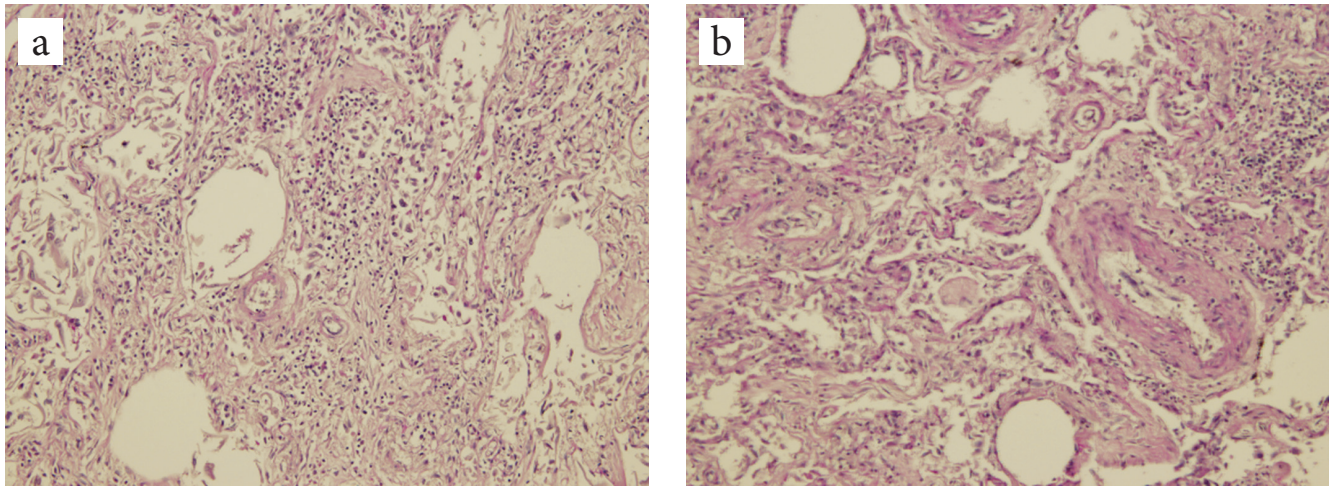

Figure 2 a,b. Different characteristics of postinflammatory lung fibrosis with concomitant unspecific lymphocyte infiltration, alveolitis, desquamated alveolar macrophages and vesicular emphysema.

form of extensive fibrosis and destructive inflammatory processes, could be detected, so far ascertainable after just eight days of drug intake, appears all the more remarkable. The frequency of occurrence of pulmonary fibrosis is stated to be very rare (< 1/10,000 patients) [11].

Since Nitrofurantoin induced lung damage is a diagnose by exclusion, thoroughly initial workup is crucial. This includes full blood count, arterial blood count, chest X-ray and pulmonary function test. Further investigations like high resolution computed tomography HRCT, bronchoalveolar lavage and cytology are of overall importance to rule out acute lung injury of different etiology.

The histopathological findings include bronchiolitis obliterans organizing pneumonia and eosinophilic pneumonia. Chest radiographs demonstrate bilateral scattered heterogonous and homogenous opacities.

The main concern of treatment is stopping the triggering agent. In serious cases mechanical ventilation can become mandatory. The role of systemic corticosteroids remains unclear.

In conclusion, drug-induced lung injury is a frequently reported side effect of our medical treatment, which should not been misdiagnosed. It can present with mild symptoms, but in serious cases like in ours, the underlying disease in combination with secondary complications can result in fatal outcome. Early recognition is very important.

Taking a careful drug history is crucial for patients with unexplained interstitial lung disease.

Beyond stopping the triggering substance and supporting lung function, there is no well-established treatment concept for substance-induced interstitial lung injury.

Conflict of interest

The authors declare that they have no conflict of interest.

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