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CASE STUDY

Ciprofloxacin-induced acute interstitial pneumonitis

D. Steiger*, L. Bubendorf#, M. Oberholzer#, M. Tamm¶, J.D. Leuppi¶

Ciprofloxacin-induced acute interstitial pneumonitis. D. Steiger, L. Bubendorf, M. Oberholzer, M. Tamm, J.D. Leuppi. ©ERS Journals Ltd 2004.

ABSTRACT: The current authors present the case of a 68-yr-old female patient who developed severe respiratory failure after medication with ciprofloxacin for acute urinary tract infection.

A chronic subdural haematoma was surgical evacuated. Postoperatively, an acute urinary tract infection was treated with ciprofloxacin. Six days later, C-reactive protein was rising and the patient was suffering from intermittent high fever, dyspnoea and severe hypoxaemia. The high-resolution-computed tomography (HRCT) showed an interstitial lung disease in the anterior upper lobe on the left side as well as in the lingula. Assuming a bacterial infection amoxyl/clavulanic acid was started which did not improve the clinical symptoms. Bronchoalveolar lavage revealed a marked lymphocytosis (87%). Analysis for typical bacterial infections, *Tuberculosis*, *Mycoplasma*, *Chlamydia* and *Legionella* spp. were all negative.

Another HRCT scan was made because of worsening of symptoms and this showed rapidly progressive infiltrates in most lobes. An open lingular biopsy showed an interstitial lymphoplasmocytotic infiltrate with some eosinophilic granulocytes and a few scattered giant cell granulomas, consistent with hypersensitivity pneumonitis. The patient's symptoms rapidly improved with systemic corticosteroid therapy and another HRCT scan revealed complete remission of pulmonary infiltrates.

Ciprofloxacin can induce interstitial pneumonitis with acute respiratory failure. This is an important fact considering that ciprofloxacin is a widely used antibiotic agent in treatment of urinary tract infection.

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*Dept of Internal Medicine, #Dept of Pathology and ¶Respiratory Medicine, Dept of Internal Medicine, University Hospital, Basel, Switzerland.

Correspondence: J.D. Leuppi
Respiratory Medicine
Dept of Internal Medicine
University Hospital
Petersgraben 4
CH-4031 Basel
Switzerland
Fax: 41 612654587
E-mail: jleuppi@uhbs.ch

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Interstitial lung disease is a known but rather rarely documented drug side-effect [1]. It is difficult to estimate the exact frequency of drug-induced interstitial lung disease and any estimate of it is probably an underestimate because of underdiagnosis, subclinical forms and lack of systematic notification to centralised drug-monitoring agencies. Cases of acute interstitial lung disease due to various drugs have been reported including amiodarone, nilutamide, ergoline drugs, methotrexate, bleomycin, acebutolol, valproate, carbamazepine and Nitrofurantoin [1]. The current study presents a case of a 68-yr-old female patient who developed severe respiratory failure after medication with ciprofloxacin for acute urinary tract infection.

Case report

68-yr-old female patient had been orally anticoagulated with phenprocoumon because of a right total knee replacement. Unfortunately, a chronic subdural haematoma had developed, and a surgical haematoma evacuation had to be performed. The postoperative recovery was initially good. An acute urinary tract infection was treated with oral ciprofloxacin (500 mg *b.i.d*) from the postoperative days 16 to 21. On day 20, a deep venous thrombosis occurred requiring therapy with low molecular heparin in intermediate dose (7500 U *s.c.* daily).

On day 22, C-reactive protein was rising reaching 161 $mg \cdot L^{-1}$ on day 30, associated with intermittent high fever (39–40°C), dyspnoea and mild leukocytosis. Blood gas analysis showed severe hypoxaemia (5.2 kPa). High-resolution-computed tomography (HRCT) on day 23 showed interstitial lung disease in the anterior upper lobe on the left side as well as in the lingula. Assuming a bacterial infection amoxyl/clavulanic acid was started (day 23–29) which did not improve clinical symptoms.

Bronchoalveolar lavage (BAL) was performed on day 30 revealing a marked lymphocytosis (87%; CD4/CD8 ratio: 5.6). Analysis for typical bacterial infections, *Tuberculosis, Mycoplasma, Chlamydia* and *Legionella* spp. were all negative. Another HRCT scan was made because of worsening of symptoms and this showed rapidly progressive infiltrates in most lobes (fig. 1). Antibiotic treatment was then switched to clarithromycin and cefepime.

On day 31, an open lingular biopsy was undertaken before administration of intravenous steroids (solumedrol 3×40 mg daily). Histology revealed an interstitial lymphoplasmocytic infiltrate with some eosinophilic granulocytes and a few scattered giant cell granulomas, consistent with hypersensity pneumonitis (fig. 2).

After two days (day 33), antibiotic therapy was stopped and oral steroids were continued (prednisone 50 mg daily). The patient's symptoms rapidly improved. An HRCT scan on day 41 (fig. 3) revealed complete remission of pulmonary infiltrates. Blood gas analysis normalised and lung function tests showed the same degree of obstructive lung disease as had already been documented in the patient's medical files in 1993.

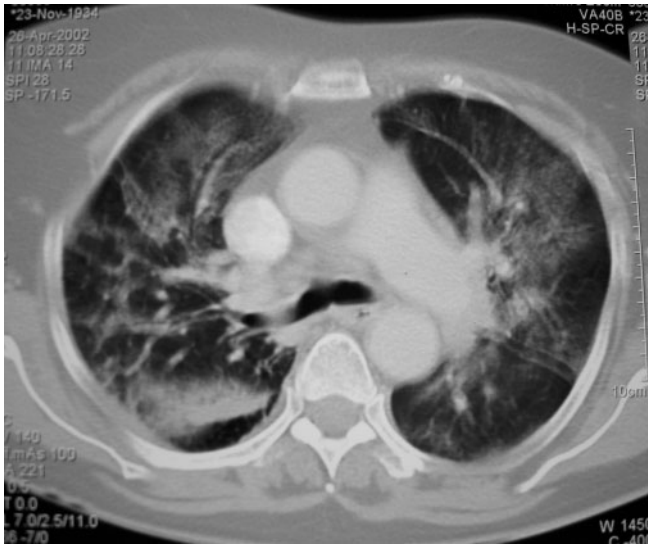

Fig. 1. – High resolution computed tomography scan on day 30 which shows rapidly progressive infiltrates in practically all lobes.

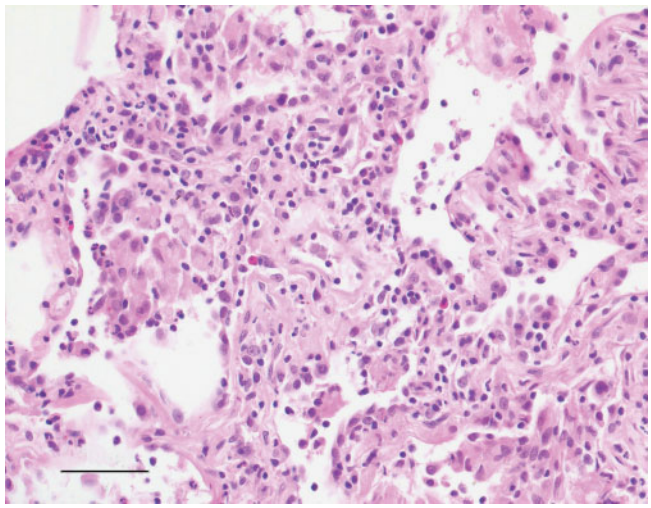

Fig. 2. – Histology showing alveolar lymphoplasmocytic infiltrate of the alveolar septa with some scattered eosinophilic granulocytes and intra-alveolar accumulation of macrophages, consistent with hypersensitivity pneumonitis (haematoxylin-eosin staining). Scale bar=50 μm.

On day 50, the patient was discharged in a good general condition, and oral steroids were slowly tapered.

Discussion

To the best of the authors′ knowledge this is the first reported case of acute interstitial pneumonitis due to ciprofloxacin. Nitrofurantoin, a related drug, has been shown to be associated with diffuse alveolar damage, interstitial fibrosis, vasculitis and bronchiolitis obliterans-organising pneumonia as well as pulmonary haemorrhage when administered for the long-term prevention of recurrent urinary tract infections [2]. A final common toxic pathway has not been found and a difference has been made between an acute and chronic clinical pattern. Hypersensitivity reactions (type I or III) may be responsible for the acute pattern whereas the chronic pattern may be caused by other allergic or toxic mechanisms (hydroxyl radical generation with subsequent free oxidant damage). Short drug exposure seems to induce acute clinical patterns whereas long-term intake seems to be related to chronic clinical patterns [3]. There is some evidence that fibroblasts can be activated for instance by bleomycin directly and indirectly by bleomycin-induced cytokines such as tumour necrosis factor-α [4]. However for most drugs, including nitrofurantoin, there is no apparent role of dose or duration of treatment in relation to the likelihood of developing adverse effects, *i.e.* development remains largely unexpected and idiosyncratic [1]. The patient presented with an acute pattern: dyspnoea, fever and severe hypoxaemia. Radiological presentation was also similar to earlier reports including rapid resolution under steroid therapy [5]. The patient showed marked lymphocytosis in BAL and a lack of peripheral eosinophilia. Lymphocytosis is believed to indicate favourable prognosis and peripheral eosinophilia occurs in 20–30% of acute clinical courses [3]. The high CD4/CD8 ratio of 5.6 found in this patient is unusual, since drug-induced hypersensitivity reactions of the lung typically cause low CD4/CD8 ratios [3]. However, interstitial lung disease secondary to drugs can also be associated with a high CD4/CD8 ratio as shown for nitrofurantoin and methotrexate [6]. A sarcoidosis can be excluded in this patient based on clinical course, radiological findings, and the histological changes.

SUZUKI *et al.* [7] described a case of Legionella pneumonia followed by interstitial lung disease possibly caused by a ciproxin-related drug: the patient had been switched to levofloxacin, clarithromycin and minocycline because of intolerance to rifampicin and erythromycin. However, it is impossible to prove an etiological relationship between levofloxacin and infiltrative lung disease because too many drugs had been switched within too short a time period in that case.

A lymphocyte stimulation and transformation test after contact with ciprofloxacin was negative in the patient. This might weaken the current authors′ hypothesis. However, a negative transformation result can not sufficiently exclude presence of an etiological relationship [8]. Based on the clinical, radiological and histological evidence, the current authors nevertheless conclude that the patient suffered a ciprofloxacin-induced interstitial pneumonitis. The only change in treatment was ciprofloxacin for urinary tract infection apart from heparin. Heparin is most unlikely to have been the

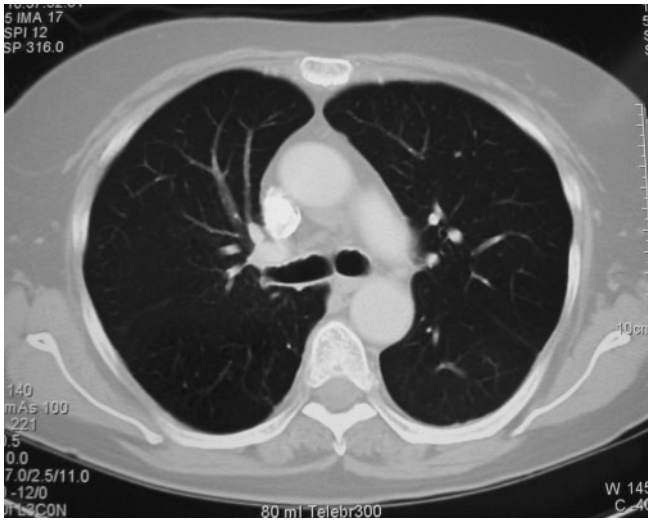

Fig. 3. – High resolution computed tomography scan on day 41 revealing a complete normalisation of pulmonary infiltrates.

culprit because the drug was introduced only 2 days before the patient started to deteriorate.

In summary, ciprofloxacin can induce interstitial pneumonitis with acute respiratory failure. This is an important fact, considering that ciprofloxacin is a widely used antibiotic agent in the treatment of urinary tract infection.

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