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CASE STUDY

Pulmonary toxicity with mefloquine

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Pulmonary toxicity with mefloquine. E. Udry, F. Bailly, M. Dusmet, P. Schnyder, R. Lemoine, J.W. Fitting. ©ERS Journals Ltd 2001.

ABSTRACT: This report presents a case of acute lung injury developing within hours after administration of mefloquine for a low-level *Plasmodium falciparum* malaria, which was persistent despite halofantrine therapy. Extensive microbiological investigation remained negative and video-assisted thoracoscopic lung biopsy demonstrated diffuse alveolar damage. The evolution was favourable without treatment.

This is the second report of acute lung injury and diffuse alveolar damage caused by mefloquine. Glucose-6-phosphate dehydrogenase deficiency was present in the former case and was thought to contribute to the lung injury. However, glucose-phosphate dehydrogenase was normal in the present case, suggesting that it is not a predisposing condition to the lung injury.

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Mefloquine is used as prophylaxis or treatment for malaria in areas where chloroquine-resistant malaria is present. Although considered a relatively safe agent, its side-effects include neuropsychiatric reactions, cutaneous lesions, bone marrow toxicity, and gastrointestinal symptoms. Here, the authors report a case of pulmonary toxicity following mefloquine administration.

Case report

A 53-yr-old geologist returned to Switzerland from New Guinea after working there for 6 weeks in the countryside. He had a previous history of one episode of malaria, hepatitis A, and renal tuberculosis treated with adequate therapy. His recent health had been good until the present episode.

Eight days after his arrival in Switzerland, he developed a high fever and, suspecting malaria, started himself on halofantrine 500 mg *q.i.d.* for 48 h together with paracetamol. The fever stopped, but reappeared 1 week later with spikes every 48 h. Nineteen days after the first febrile episode, he went to an emergency department where the diagnosis of malaria with *Plasmodium falciparum* was established with a parasitaemia of 0.2%. He received a total dose of 1,500 mg mefloquine over 24 h. During the next night he had fever, cough and moderate dyspnoea and was then admitted to the hospital.

On admission, the patient was in poor general condition: thin, blood pressure 90/50 mmHg, heart rate 80 min^{-1}, tympanic temperature 38°C, and respiratory rate 20 min^{-1}. On examination, lung auscultation revealed fine crackles laterally on the left. Laboratory findings showed a low haemoglobin level (1.04 $g \cdot L^{-1}$), a haematocrit of 30%, and a leukocyte count of 15×10^9 L^{-1} with left deviation (63% segmented neutrophils, 10% nonsegmented neutrophils and 20% lymphocytes). C-reactive protein was 188 $mg \cdot L^{-1}$ and lactic dehydrogenase 878 $U \cdot L^{-1}$. Hepatic and renal function tests were within normal limits. *P. falciparum* trophozoites were found in 0.1% of erythrocytes. The chest radiograph showed a slight infiltrate in the mid-field of the left lung.

The diagnosis was that *P. falciparum* malaria was persistent despite halofantrine treatment. The patient received one loading dose of parenteral quinine (20 $mg \cdot kg^{-1}$) then 10 $mg \cdot kg^{-1}$ *q.i.d.*, followed by per-oral quinine sulphate 650 mg *t.i.d.* for 5 days and doxycycline 100 mg *b.i.d.* for 5 days. Because of diarrhoea, ceftriaxone 2 $g \cdot day^{-1}$ was empirically added.

Two days later, the patient's condition deteriorated; he was dyspnoeic at rest and bilateral radiological pulmonary infiltrates increased markedly (fig. 1). The arterial blood gases revealed severe hypoxaemia (oxygen tension in arterial blood (P_{a,O_2}) 6.3 kPa (47 mmHg), carbon dioxide tension in arterial blood (P_{a,CO_2}) 4.4 kPa (33 mmHg), pH 7.45, bicarbonate 23 mM). Because of a positive screening test (enzyme-linked immunosorbent assay (ELISA)+) for human immunodeficiency virus (HIV), *Pneumocystis carinii* pneumonia was suspected and a bronchoscopy with bronchoalveolar lavage (BAL) was performed.

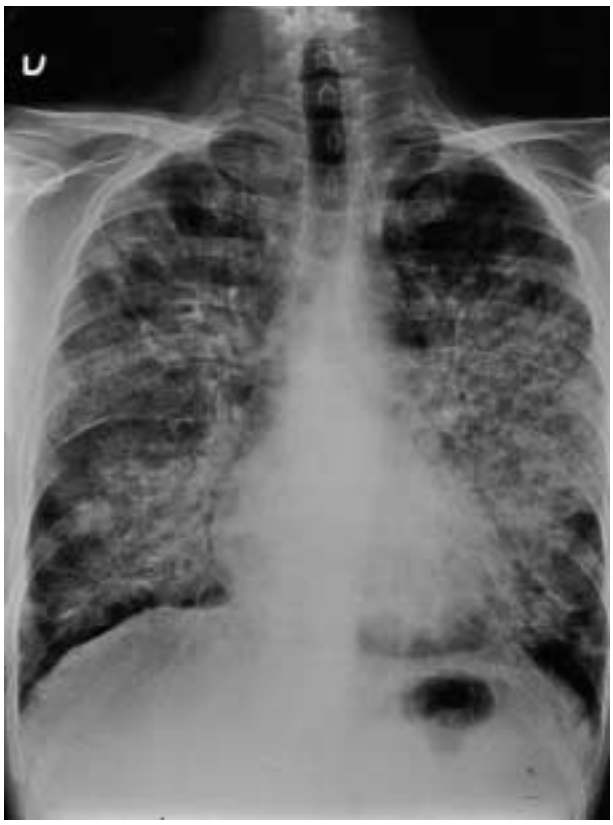

Fig. 1. – Posteroanterior chest radiograph showing diffuse confluent infiltrates.

Tracheobronchial mucosa appeared normal and without secretions. BAL fluid showed an increased number of cells ($82\times10^{6}\cdot L^{-1}$), with 43% neutrophils, 38.5% alveolar macrophages, 14.5% lymphocytes, 1.5% nonsegmented neutrophils, 1% eosinophils, and 1% basophils. Trimethoprim-sulfamethoxazole was started empirically after bronchoscopy, but was stopped after 48 h because *P. carinii* were absent in the BAL and the Western blot for HIV was negative. The patient's condition continued to deteriorate with increasing tachypnoea, arterial desaturation and increasing pulmonary infiltrate. Computed tomography (CT) confirmed the presence of diffuse bilateral pulmonary infiltrates of ground-glass attenuation and mild thickening of interlobular septa (fig. 2). At that time, all microbiological investigations remained negative in the sputum (direct exam and culture for bacteria, fungi, mycobacteria, polymerase chain reaction (PCR) for Legionella), blood (cultures, serology for toxoplasmosis and Borrelia, buffy coat for cytomegalovirus, antigen for Cryptoccocus), urine (bacteria culture, antigen for Legionella), stool (enteroparasites, pathogenic bacteria, viruses), and BAL fluid (direct exam and culture for bacteria, fungi, mycobacteria, Legionella). Seven days after admission, a video-assisted thoracoscopic lung biopsy was performed, which showed hyaline membranes lining the alveolar spaces with sloughed type-2 pneumocytes and a discrete interstitial thickening with lymphocytic infiltrates, consistent with diffuse alveolar damage (DAD)

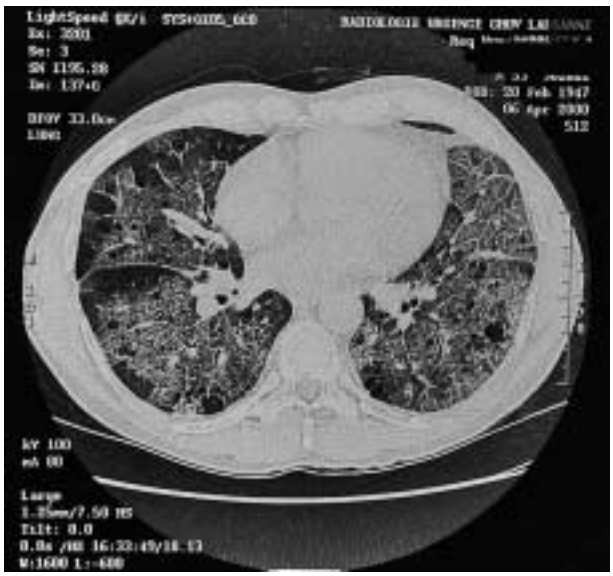

Fig. 2. – Chest computed tomography showing diffuse ground-glass pulmonary infiltrates and mild thickening of the interlobular septa.

(fig. 3). Lung biopsy and pleural fluid did not show any bacteria or fungi at histology or culture, viruses at culture, parasites at histology or toxoplasmosis by PCR.

Without further treatment, the patient's clinical condition gradually improved with regression of the radiological infiltrates. Twelve days after admission, he was able to perform lung function tests which showed a forced vital capacity (FVC) of 3.45 L (79% of predicted) and a carbon monoxide diffusing capacity of the lung ($D_{L,CO}$) of 3.8 $mmol\cdot kPa^{-1}\cdot min^{-1}$ (40% pred). Arterial blood gases had also improved: P_{a,O_2} 8.5 kPa (64 mmHg), P_{a,CO_2} 4.5 kPa (34 mmHg), pH 7.46, bicarbonate 24 $mmol\cdot L^{-1}$. One month later, the patient was again in good condition, with only a minimal residual pulmonary infiltrate. The FVC was

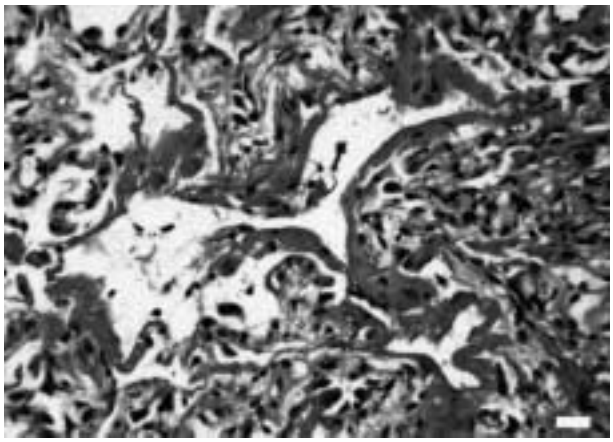

Fig. 3. – Histology of lung biopsy. The surface of the alveolar walls is lined by abundant fibrin deposits, with the typical aspect of hyaline membranes; the histological picture corresponds to that of diffuse alveolar damage (Internal scale bar=70 μm; haematoxylin and eosin)

normal (106% pred), whereas $D_{L,CO}$ was still subnormal (60% pred). Two months later the radiological pulmonary infiltrates disappeared completely, whereas the $D_{L,CO}$ remained 64% pred.

Discussion

This patient developed rapidly, evolving diffuse lung infiltrates and hypoxaemia (P_{a,O_2}/inspiratory oxygen fraction (F_{I,O_2})=233) corresponding to an acute lung injury according to the criteria of the American-European Consensus Conference on acute respiratory distress syndrome (ARDS) ($P_{a,O_2}/F_{I,O_2}$ <300, bilateral opacities compatible with pulmonary oedema, and pulmonary artery occlusion pressure <18 mmHg or no clinical evidence of left atrial hypertension) [1]. The histopathological picture was consistent with DAD, thus opening a large differential diagnosis [2, 3].

An infectious origin other than malaria could not be documented, as extensive microbiological investigations remained negative. Furthermore, the histological picture showed neither neutrophilic infiltrates or viral inclusions. Acute lung injury can occur secondary to malaria, but typically, only in the more severe forms of the disease, reflected by high acute physiological scores [4–7]. The patient had only a low parasitaemia, which disappeared on the second day of hospital admission. Furthermore, he did not present any of the criteria of severe malaria, such as cerebral malaria with coma or seizures, severe anaemia, oliguric renal failure, hypoglycaemia, malignant hyperthermia, acidaemia or acidosis, circulatory collapse or shock, spontaneous bleeding, disseminated intravascular coagulation, or jaundice [8, 9]. Acute lung injury in malaria is also usually associated with a longer time interval to the initiation of adequate antimalarial therapy [10]. Finally, the histological picture did not show any extravascular red blood cells, parasites within red blood cells or neutrophilic infiltrates. Thus, acute lung injury in this patient could not be considered to result from malaria.

On the basis of history and clinical examination there was no clue suggesting a toxic origin (such as one caused by smoke, paraquat, ethylchlorvynol, or illicit drugs), prior radiotherapy, collagen vascular disorders, or the other usual causes of ARDS. The Hamman-Rich syndrome could be ruled out by the spontaneously favourable evolution. A drug-induced origin remained the most likely hypothesis. Among the different medications the patient took before admission (halofantrine, paracetamol, mefloquine) and in the hospital (quinine, doxycycline and ceftriaxone), the only ones showing a clear time relation with the respiratory symptoms were mefloquine and paracetamol.

Recently, DRENT [11] described a case of drug-induced pneumonia due to mefloquine in a patient with latent hemizygote glucose-phosphate dehydrogenase deficiency. The patient became dyspnoeic and febrile 2 days after taking mefloquine. Chest radiograph showed diffuse nonspecific interstitial infiltrates and lung CT showed diffuse opacities of ground-glass attenuation. All cultures remained sterile and transbronchial lung biopsy revealed DAD. The patient was treated with systemic corticosteroids (initially prednisone, 50 mg daily) and recovered completely. This patient was reported to present hemizygote deficiency of glucose-phosphate dehydrogenase. The author hypothesized that the severe lung injury resulted from a failure to induce glutathione redox cycle enzyme and from oxidative stress [11]. The quantitative dosage of glucose-6-phosphate dehydrogenase was normal in the present authors' patient, suggesting that the finding of glucose-6-phosphate dehydrogenase deficiency in the case report of DRENT [11] could be incidental. The present authors declined to rechallenge their patient by mefloquine.

In summary, this acute lung injury with diffuse alveolar damage was attributed to mefloquine, after ruling out all other possible causes. In view of the similarity between this case and the recent one reported by DRENT [11], the authors recommend that mefloquine should be added to the list of drugs that are potentially harmful to the lungs.

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