BRIEF COMMUNICATIONS

Mefloquine-Induced Pneumonitis

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Mefloquine is indicated as oral treatment and as prophylaxis for malaria in areas where chloroquine-resistant malaria is present. Gastrointestinal and neuropsychiatric side effects of mefloquine are well known. More severe neuropsychiatric disorders such as psychosis, depression, hallucinations, and seizures are also reported in the literature. We are reporting a case of drug-induced pneumonia due to mefloquine. This diagnosis was confirmed 4 months after the adverse event, after restarting the same malaria prophylaxis, which could be considered as an unintentional provocation test. This is the third case report in the literature of acute lung injury caused by mefloquine.

Case Report

A 60-year-old Caucasian female, resident of Belgium, planned to visit Kenya and commenced mefloquine 250 mg (prophylactic dose of one tablet of 250 mg once a wk), 3 weeks before traveling. The shelf life of the mefloquine lot was not expired. She had never taken malaria prophylaxis before. She never smoked, there was no exposure to pet animals, and she had no pulmonary or allergic history. She was using daily chronic medication: low-dose aspirin, a beta-adrenergic blocker (bisoprolol fumarate), and a fibrate (ciprofibratum) for atherosclerosis, hypertension, and hyperlipidemia, respectively.

One day after the first mefloquine 250 mg intake, she developed high fever and chills, and empiric antibiotic treatment was started. Four days later, she was admitted to the local hospital because of severe fever, progressive shortness of breath, nonproductive cough, myalgia, and headaches.

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On admission, she looked cyanotic and was tachycardic. Her temperature was 38.5°C. There were bilateral crepitations over the lungs but no wheezes.

Laboratory tests showed a leukocytosis [white blood cell count: 19,900 cells/μL (normal range: 4.3–10 cells/μL) with 71% neutrophils, 18% lymphocytes, and no eosinophils], an elevated C-reactive protein [CRP: 194 mg/dL (normal range: <3 mg/dL)], and a raised lactate dehydrogenase (LDH). Blood and sputum cultures did not grow any organism. A chest radiograph showed bilateral interstitial infiltrates.

Without additional treatment, she improved slowly and was discharged 20 days after admission. The considered diagnosis at that point was diffuse interstitial pneumonia (IP) of unknown origin (bacterial, viral, or drug-induced). She canceled her trip to Kenya at that moment.

Four months later, she restarted by herself on the same malaria prophylaxis before traveling to Kenya. In a similar fashion to the first episode, she developed a high fever the day after, and exactly 3 days later, she became critically ill, requiring admission to an intensive care unit because of severe respiratory distress. Laboratory findings revealed

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similar results (leukocytosis, a raised CRP, and elevated LDH). There was severe hypoxemia (pO_2: 45 mm Hg, pCO_2: 32 mm Hg, pH: 7.44) on arterial blood gas analysis, and the chest radiographs showed bilateral severely infiltrated lungs. High-resolution computed tomography (CT) confirmed the presence of diffuse pulmonary infiltration and ground-glass attenuation. All the microbiological investigations remained negative. She responded well clinically and radiologically after starting corticosteroids.

Her lung function tests showed an impaired carbon monoxide–diffusing capacity of the lung (DLCO) (lower than 40% of predicted).

Discussion

Mefloquine is a quinoline-methanol compound structurally similar to quinine. At prophylactic doses, risks of serious toxicity are about 1 in 10,000, similar to chloroquine. Doses used in therapy are more commonly associated with nausea, dizziness, fatigue, mental confusion, and sleep loss. Psychosis, encephalopathy, and convulsions are seen in about 1 in 1,200 to 1,700 patients.[1] Mefloquine-associated pulmonary toxicity is very exceptional.

Until now, only two cases of mefloquine-induced pneumonia have been published. In 1998, Drent described a case of acute lung injury due to prophylactic mefloquine (total dose of 1,000 mg) in a 64-year-old patient with hemizygote glucose-phosphate dehydrogenase deficiency (G6PD).[2] Subsequently, Udry and colleagues published in 2001 a second case of acute lung injury due to mefloquine. The 53-year-old patient was treated with a full-day course of therapeutic mefloquine (total dose of 1,500 mg) before admission for a low-level *Plasmodium falciparum* malaria, which was still persistent 1 week after self-treatment with halofantrine therapy.[3]

To summarize these three cases of mefloquine-induced pneumonitis, we can note that there was a clear temporal relationship between pill intake and the respiratory symptoms (1 day to 3 weeks). The patients had fever, symptoms of respiratory distress, and a nonproductive cough. Serum leukocytes (with high neutrophil count and without eosinophils), CRP, and LDH were all raised. Radiographic imaging demonstrated bilateral lung infiltrates. Airspace consolidation and ground-glass attenuation were seen on CT scans. In two cases, a bronchoalveolar lavage (BAL) was performed, and the fluid showed raised neutrophils and foamy macrophages. In one patient, lung biopsy was performed and revealed diffuse alveolar damage (DAD). Two patients were rechallenged with mefloquine and developed severe respiratory symptoms. In these two patients, systemic corticosteroids were prescribed with good clinical and radiological response. In Udry's patient and for the first episode of our patient cessation of the provocative agent alone was enough to improve the patient's clinical condition over time. In two patients (Udry's patient and ours), DLCO remained impaired over time.

Various drugs are associated with adverse respiratory disorders (ADR) ranging in severity from mild to severe and even fatal. The diagnosis of drug-induced pulmonary toxicity is often missed because the possibility of a drug reaction was not given appropriate consideration.[4] The diagnostic approach to patients must be dictated by the specific clinical findings and the setting in which they occur. Every patient should undergo a thorough history, and a high index of suspicion for drug-induced syndromes is required. When a clear temporal relationship between the intake of the drug and the respiratory symptoms can be made, the diagnosis of drug-induced pneumonitis has to be considered.[5] Suspected provocative drugs related to pulmonary toxicity can be checked on the Web site (www.pneumotox.com). In our case, patient had also taken chronically aspirin, bisoprolol, and ciprofibratum. Drug-induced pneumonitis with these drugs are not reported in the literature or on the Web site.

ADRs present several hours to 6 weeks after intake of the responsible drug. Patients develop fever, a nonproductive cough, dyspnea, crackles upon auscultation, and/or a rash. Laboratory findings show an eosinophilia or leukocytosis.[5] Raised immunoglobulin E can usually be found.[6] Radiographic imaging of the chest demonstrates bilateral patchy infiltrates. In a retrospective Japanese study, the use of high-resolution CT was helpful in making a diagnosis. The predominant CT findings in antibiotic-induced pneumonitis were patchy ground-glass attenuation with centrilobular opacities and interlobular septal lines.[7] More invasive diagnostic tests, like BAL or video-assisted thoracoscopic surgery, are not needed when the history and associated findings identify a provocative agent, such as a medication, but are useful in ruling out other lung diseases. Typical findings for BAL fluid in drug-induced pneumonitis are raised foamy macrophages and lymphocytosis. The neutrophils and the eosiniphils in the BAL fluid can also be elevated. The CD4/CD8 ratio is usually abnormal.[6,8–9] These findings are nonspecific. Biopsy of the lung in drug-induced pneumonitis can show an eosinophilic pneumonia, an IP, bronchiolitis obliterans

organizing pneumonia (BOOP), a hypersensitivity reaction, or other disorders, like DAD.

A positive provocation test (rechallenge test) is diagnostic but not advisable. A drug lymphocyte stimulation test or a skin patch test with the causative agent are helpful in making the diagnosis.[5–6] In most patients, the pulmonary abnormalities disappear over time after cessation of the causative drug.

Empiric corticosteroids are indicated when a patient is acutely hypoxemic and in respiratory distress. The clinical response to corticosteroids in particular cases is very good.[10]

The most common pulmonary hypersensitivity reaction caused by antimicrobial agents (beta-lactam and sulfa antibiotics, antimalarials, and antituberculosis drugs) typically presents as pulmonary infiltrates with eosinophilia [pulmonary interstitial emphysema (PIE) syndrome, also known as eosinophilic pneumonia], although IP, BOOP, and DAD are also related.[4,11] The defining characteristics needed for the diagnosis of pulmonary eosinophilia include either serum eosinophilia with radiologically or tomographically identified pulmonary abnormalities, lung tissue eosinophilia demonstrated in transbronchial or open lung biopsies, or increased eosinophils in BAL fluid.[10,12–13] In the three presented cases with mefloquine-induced pneumonitis, peripheral eosinophils were absent. The eosinophils in the BAL fluid, performed in two patients, were not raised. The biopsy of the lung, performed in one patient, did not reveal an eosinophilic inflammation. Although antibiotics and antimalarials are most often associated with PIE syndrome,[13] we could not show a relationship between mefloquine and raised peripheral and/or pulmonary eosinophils in our case, nor in the two other case reports in the literature. A specific relationship between mefloquine and the PIE syndrome cannot be found after retrospective evaluation of these three cases. Another syndrome, possibly a hypersensitivity reaction, is likely responsible for this mefloquine-related pneumonitis. It is advisable after a severe drug-induced event to avoid the provocative agent and to use other antimalarials for prophylaxis and/or therapy.

Retrospectively, the limitations of our case report are that we did not determined serum tryptase. High levels of tryptase are suggestive for drug-induced phenomena. We did not check drug levels of mefloquine at the acute event, although drug interactions with aspirin, ciprofibratum, and bisoprolol were not known. Another shortcoming is that we did not reanalyze the lot quality of the used package of mefloquine for impurities.

In summary, travelers will be exposed to prophylactic and therapeutic doses of mefloquine. All clinicians prescribing mefloquine must be aware of the uncommon pulmonary toxicity of this drug.

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Declaration of Interests

The authors state that they have no conflicts of interest.

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