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Case Report

Acute eosinophilic pneumonia associated with mefloquine prophylaxis: A case report

Francesco Virzì [a,1], Giuseppe Giacopelli [a,1], Paolo Tutone [a], Luigi Profera [c], Antonino Giarratano [b,c], Santi Maurizio Raineri [b,c], Sandro Tomasello [a,1], Giuseppe Accurso [c,*,1]

[a] Unit of Anesthesia, Intensive Care, and Hyperbaric Medicine, Civico Emergency Hospital, Sicily, Partinico, Italy
[b] Department of Precision Medicine in Medical, Surgical and Critical Care, University of Palermo, Sicily, Italy
[c] Department of Anaesthesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, Sicily, Palermo, Italy

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ABSTRACT

Background: Eosinophilic pneumonia is a rare but potentially life-threatening condition characterized by eosinophilic infiltration of the lung parenchyma, which can present as acute respiratory failure. Drug-induced eosinophilic pneumonia (DIEP) has been associated with several medications, though the pathophysiological mechanisms remain incompletely understood. Among antimalarial agents, mefloquine has rarely been implicated in severe pulmonary adverse effects.
Case presentation: We report the case of a 34-year-old previously healthy female who developed acute respiratory failure after completing a prophylactic regimen of mefloquine for malaria prevention. The patient initially presented with fever, dyspnea, and hypoxemia, rapidly progressing to severe respiratory distress requiring invasive mechanical ventilation. Laboratory tests revealed marked eosinophilia, while thoracic computed tomography (CT) demonstrated diffuse ground-glass opacities and nodular infiltrates. Bronchoalveolar lavage (BAL) was positive for Rhinovirus, suggesting a possible interplay between drug-induced hypersensitivity and viral infection. Following corticosteroid therapy and supportive care, the patient's condition improved, with resolution of eosinophilia and radiological abnormalities.
Discussion: This case highlights the need for heightened clinical suspicion of mefloquine-induced eosinophilic pneumonia in patients presenting with unexplained respiratory symptoms following antimalarial prophylaxis. The pathogenesis may involve immune-mediated reactions and oxidative stress, potentially exacerbated by concurrent infections.
Conclusion: Mefloquine should be considered a potential cause of acute eosinophilic pneumonia, particularly in patients with recent drug exposure. Early recognition and timely management, including drug discontinuation and corticosteroid therapy, are crucial to preventing severe complications and ensuring favorable outcomes.

* Corresponding author.
E-mail address: giuseppe.accurso@policlinico.pa.it (G. Accurso).
[1] *These authors contributed equally to this work.*

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1. Introduction

Eosinophilic pneumonia, a complex condition with a diverse range of etiologies, underscores the necessity of a multidisciplinary approach. The accumulation of eosinophilic infiltrates in the lung parenchyma, with or without associated peripheral blood eosinophilia, presents a diagnostic challenge that can only be met through the collaboration of an expert team [1].

Diagnosis and treatment of eosinophilic pneumonia require a comprehensive approach, including clinical, laboratory, and radiological investigations, and in some cases, bronchoscopy with bronchoalveolar lavage (BAL) or lung biopsy. The importance of careful follow-up cannot be overstated, as it is essential for monitoring the patient's response to therapy and preventing relapses [2].

While rare, eosinophilic pneumonia is a crucial differential diagnosis in patients with acute respiratory symptoms and a radiological pattern suggestive of pulmonary infiltrates [3]. Emphasizing the need for early recognition and appropriate therapeutic intervention is vital, as it can significantly impact patient outcomes [3].

Mefloquine is an antimalarial drug primarily indicated for malaria chemoprophylaxis in travellers to endemic areas with a high prevalence of *Plasmodium falciparum* strains resistant to other antimalarials. Prophylaxis with mefloquine requires initiation at least 10 days before departure, with a weekly dose of approximately 5 mg/kg of body weight. The treatment regimen must continue throughout the stay in the endemic area and for four weeks after returning [4].

Generally, the drug is well tolerated, but in a minority of cases, adverse reactions may occur, including gastrointestinal disturbances, psychiatric symptoms (anxiety, insomnia, depression, psychotic episodes), cardiovascular effects, and respiratory complications [5].

Among the more severe adverse reactions, although rare, bone marrow toxicity with haematological alterations has been reported. Some of these reactions can occur even after discontinuation of the drug, necessitating prolonged clinical monitoring [6].

2. Case report

A 34-year-old female patient, previously in good health and without significant chronic diseases, was admitted to the Emergency Department of the Civico Hospital in Partinico due to acute respiratory symptoms. Her medical history was negative for chronic diseases, with regular vaccinations and an active lifestyle (outdoor running). The only relevant anamnesis was a work-related stay in the Congo two months earlier, for which she had undergone malaria prophylaxis with mefloquine 250 mg once a week, continued for four weeks after returning home.

Three days before hospitalization, the patient developed a fever and worsening dyspnea. Upon arrival at the Emergency Department, she appeared in compromised general condition, with asthenia, respiratory distress, tachypnea (30 breaths/min), tachycardia (>100 bpm), fever (Tc 39 °C), and oxygen saturation between 88 % and 90 %, unresponsive to high-flow oxygen therapy.

Blood tests revealed leukocytosis (WBC 17.340/mm^3, neutrophils 78.1 %), elevated C-reactive protein (4.72 mg/L), increased D-dimer, and negative procalcitonin. Liver and cardiac function tests were within normal limits. Initial thoracic CT showed multiple areas of parenchymal hyperdensity with a nodular appearance and diffuse ground-glass opacities suggestive of an acute inflammatory pulmonary process (Fig. 1).

Despite high-flow oxygen therapy, respiratory failure worsened, necessitating orotracheal intubation and protective mechanical ventilation (TV 6 ml/kg PBW, respiratory rate 20 breaths/min, PEEP 10 cmH_2O mmHg, FiO_2 80 %), requiring continuous sedation and neuromuscular blockade in the intensive care unit. Microbiological tests (blood cultures, urine cultures, and BAL) were negative except for Rhinovirus/Enterovirus positivity. Empirical antimicrobial therapy with piperacillin/tazobactam 9 g IV bolus followed by 18 g continuous infusion, levofloxacin 750 mg daily, and vancomycin 2 g continuous infusion was started. Concurrently, corticosteroid therapy with prednisone 40 mg/day was added. Additional laboratory test results were obtained, including serum complement analysis, rheumatoid factor, antinuclear antibodies, antineutrophilic cytoplasmic antibodies, and immunoglobulin levels—especially

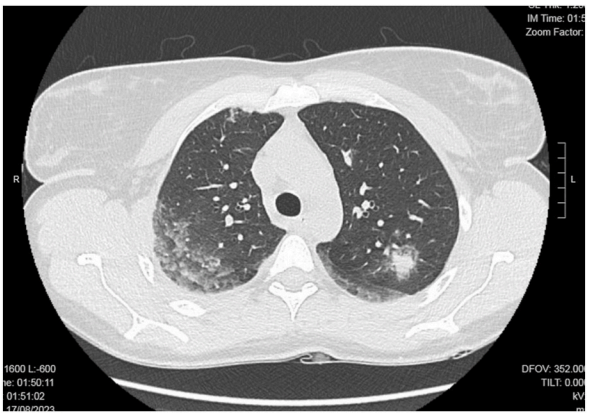

Fig. 1. High-resolution computed tomography scan of the chest shows multiple areas of parenchymal hyperdensity with a nodular appearance and diffuse ground-glass opacities.

the immunoglobulin E antibody levels for specific allergens. All tests returned negative results, except for eosinophilia, which was found at 28 %, and elevated gamma-GT levels. Tests for Strongyloides and Schistosoma were performed to rule out parasitic infections, both of which resulted in negative findings.

After one day, repeat thoracic CT showed partial resolution of the ground-glass opacities with new consolidative areas (Fig. 2). Oxygenation gradually improved, allowing for ventilatory weaning and successful extubation. One week later, the patient's clinical condition had improved; she was afebrile and peripheral blood eosinophilia had resolved. Arterial blood gases were wholly restored to normal. After a nine-day hospital stay, the patient was discharged in good clinical condition.

These findings were consistent with eosinophilic pneumonia, and since no other apparent cause was identified, a drug-related aetiology remained the most presumptive diagnosis.

Follow-up thoracic CT before discharge (Fig. 3) confirmed significant improvement in the pulmonary infiltrates. However, it's important to note that some patients may experience long-term effects or relapses, underscoring the need for continued monitoring and follow-up.

3. Discussion

Among the clinical forms, acute eosinophilic pneumonia is distinguished by its sudden onset, often accompanied by high fever, marked dyspnea, and diffuse pulmonary infiltrates detectable by thoracic imaging. In severe cases, it can progress to acute respiratory failure requiring intensive treatment [3].

The causes of eosinophilic pneumonia can be idiopathic or secondary to external factors and underlying conditions, including drug exposure, environmental toxins, neoplasms, substance abuse (such as drugs and smoking), and parasitic infections. The pathogenic mechanism remains unclear in idiopathic cases, but an aberrant immune response mediated by eosinophils is hypothesized [7].

Mefloquine hydrochloride is an effective and widely used antimalarial agent that emerged as a successor to chloroquine [4]. The drug's primary and precise mechanisms of action remain obscure. However, the most widely supported hypothesis is that mefloquine binds to high-density serum lipoproteins and is distributed to erythrocytes, interacting with stomatin (an erythrocytic membrane protein) [8]. The drug is then transferred to the intracellular parasite through a pathway to uptake exogenous phospholipids, generating deleterious effects on plasmodial structures [8].

Numerous drugs have been implicated in adverse pulmonary disorders. Eosinophilic pneumonia is regarded as a classical drug reaction, as the number of culpable medications continues to increase. The most frequently reported drugs causing eosinophilic pneumonia include 5-aminosalicylic acid, chlorpromazine, minocycline, nitrofurantoin, penicillin, sulfasalazine, and tetracycline [3, 9].

The most essential aspect of diagnosing drug-induced eosinophilic pneumonia is maintaining a high index of suspicion. Five diagnostic criteria for this disease have been proposed: exclusion of other lung diseases; a detailed history of drug exposure; clinical, imaging, BAL fluid, or tissue findings consistent with drug-induced eosinophilic lung disease; a time course compatible with drug-induced lung disease; and improvement following withdrawal of the suspected drug [7]. Our patient met four of these five criteria. The case shares several characteristics with previously reported cases of mefloquine-induced eosinophilic pneumonia [10]. However, our patient developed a more severe acute respiratory failure requiring invasive ventilatory support. This clinical progression suggests that individual responses to mefloquine may vary significantly, likely due to genetic predisposition or environmental factors.

Another aspect to consider is the pathogenic mechanism underlying the eosinophilic reaction. While previously reported cases have hypothesized the involvement of immune-mediated reactions and oxidative stress, our case further supports the hypothesis of a possible inflammatory response exacerbated by concomitant viral infections, such as the rhinovirus detected in the patient's BAL.

Relatively little is known about the mechanisms underlying drug-induced eosinophilic pneumonia. However, the disorder is thought to be mediated by specific immunologic reactions. Pulmonary adverse effects of antimalarial agents are rare, but mefloquine

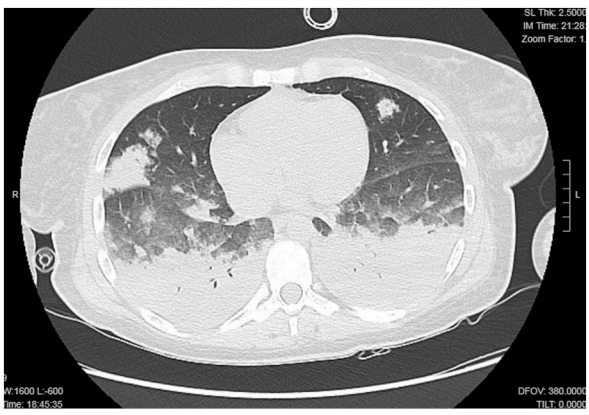

Fig. 2. High-resolution computed tomography scan of the chest shows partial resolution of the ground-glass opacities with new consolidation, and bibasal atelectasis."

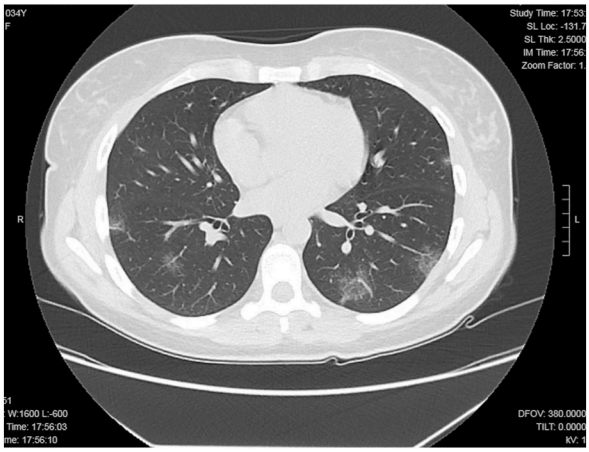

Fig. 3. High-resolution computed tomography scan of the chest reveals marked improvement, with only minimal residual subpleural infiltrates.

has been associated with various forms of lung injury, ranging from subacute cellular interstitial pneumonitis to severe acute respiratory distress syndrome.

A limitation of this case is the unavailability of eosinophil count in the BAL bronchoalveolar lavage (BAL) fluid, due to technical constraints in our laboratory. However, the diagnosis of acute eosinophilic pneumonia was established based on four out of five recognized diagnostic criteria for drug-induced forms: clinical and radiological findings, peripheral eosinophilia, and temporal association with mefloquine administration, with clinical improvement following drug discontinuation.

4. Conclusion

This case highlights the critical need for clinical vigilance in recognizing mefloquine-related adverse reactions, especially in the differential diagnosis of acute respiratory failure. Timely identification and prompt intervention are crucial to prevent severe complications and improve patient outcomes.

CRediT authorship contribution statement

Francesco Virzì: Writing – original draft. **Giuseppe Giacopelli:** Writing – original draft. **Paolo Tutone:** Conceptualization. **Luigi Profera:** Visualization, Validation. **Antonino Giarratano:** Supervision. **Santi Maurizio Raineri:** Writing – review & editing, Validation, Supervision. **Sandro Tomasello:** Supervision. **Giuseppe Accurso:** Writing – review & editing, Visualization, Validation.

Founding

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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