

Hydroxychloroquine-induced agranulocytosis in a patient with long-term rheumatoid arthritis

Edward Sames, Heather Paterson, Charles Li

Abstract

Agranulocytosis is a rare and little-known side effect of hydroxychloroquine use. This report describes the case of a 71-year-old woman with poorly controlled rheumatoid arthritis who developed agranulocytosis after several months of hydroxychloroquine therapy. She had been on several different disease-modifying antirheumatic drugs, including methotrexate and leflunomide, for her rheumatoid arthritis. Treatment became complicated following a diagnosis of leflunomide-induced pulmonary fibrosis that was discovered after an intensive care unit (ICU) admission for severe *Pseudomonas pneumonia*. All treatment was stopped apart from steroids and hydroxychloroquine. Because of persistent disabling symptoms, rituximab infusions were given, which improved the disease control. A second admission occurred after a routine blood test revealed agranulocytosis. Hydroxychloroquine was stopped, and after 24 h, she was discharged home. Blood counts returned to normal within 2 weeks of hydroxychloroquine cessation; hence, after the review of investigations, a diagnosis of hydroxychloroquine-induced agranulocytosis was made. This report considers current literature on hydroxychloroquine-induced agranulocytosis and explores the potential causes for this occurrence.

Keywords: Hydroxychloroquine, agranulocytosis, rheumatoid arthritis

Introduction

Hydroxychloroquine (Covis Pharma; Zug, Switzerland) was initially developed as an antimalarial. In rheumatoid arthritis (RA), it is thought to reduce the interaction between T helper cells and antigen-presenting macrophages that cause joint inflammation and decrease the production of proinflammatory cytokines, thus reducing the overall inflammatory response in RA (1). It can be used as a monotherapy in mild RA or in combination with other disease-modifying antirheumatic drugs. The most common side effects are skin rashes and corneal deposits. The most serious side effect is retinopathy, but this is rarely seen before 6 years of use, and is the reason why patients receiving this therapy undergo regular visual field testing (1). Informed consent was obtained from the patient for the publication of this case report.

Case Presentation

A 71-year-old woman was referred by her general practitioner following the discovery of neutropenia on a routine blood test. She had been under regular surveillance since her diagnosis of seropositive, anti-cyclic citrullinated peptide-positive erosive RA in 1983. Her past medical history included diverticulitis, Sjogren's syndrome, and iron deficiency anemia. She was an ex-smoker and lived independently with her husband.

Initially, her RA was successfully treated with gold injections for 15 years; however, in 1998, after repeated flares, the treatment was changed to oral methotrexate monotherapy. Despite dose escalation, she was unable to achieve adequate disease control, and sulfasalazine (Salazopyrin, Pfizer, Kent, United Kingdom) and hydroxychloroquine were added. However, symptoms remained uncontrolled on triple therapy, and in 2010, she was started on leflunomide (Arava, Aventis Pharma, Mumbai, India). Three months after this, she was admitted to hospital with cough, pyrexia, and worsening shortness of breath. She was diagnosed with severe pneumocystis and *Pseudomonas pneumonia* and was intubated and ventilated in the intensive care unit. She was subsequently diagnosed with pulmonary fibrosis, and both methotrexate and leflunomide were stopped. By 2012, she was on hydroxychloroquine monotherapy. Following another flare, she was started on rituximab (Rituxan, Roche, Basel, Switzerland) infusions, which improved the symptoms over the next few months. She developed anemia [hemoglobin (Hb) level 53 g/dL], which required admission for a blood transfusion. However, both colonoscopy and esophageal endoscopy failed to find the cause for this anemia. For this reason, the patient was undergoing regular blood tests, and the agranulocytosis became apparent.

At the time of her presentation for agranulocytosis, she was asymptomatic and gave no history of recent illness, unexplained fevers, night sweats, or systemic symptoms. On admission, she was hemodynamical-



Department of Rheumatology, Royal Surrey County Hospital, Guildford, United Kingdom

Address for Correspondence:
Edward Sames, Department of Rheumatology, Royal Surrey County Hospital, Guildford, United Kingdom

E-mail: edward.sames@nhs.net

Submitted: 17.03.2015

Accepted: 18.05.2015

Available Online Date: 21.08.2015

©Copyright by 2016 Medical Research and Education Association - Available online at www.eurjrheumatol.org

ly stable and afebrile. Clinically, there was no palpable lymphadenopathy, and examination of the abdomen showed no evidence of hepatosplenomegaly. Chest auscultation revealed normal heart sounds and bibasal fine inspiratory crepitations. Current medications at the time of admission were hydroxychloroquine 200 mg daily, omeprazole, and ferrous fumarate.

Blood tests on admission revealed significant neutropenia with white cell count of $2.0 \times 10^9/L$, neutrophil count of $0.10 \times 10^9/L$, Hb level of 116 g/dL, and platelet count of $401 \times 10^9/L$. Renal and liver functions, and bone profile were normal, but the C-reactive protein level was elevated at 86. Urine dip and blood cultures were negative. Both chest X-ray and abdominal X-rays done at the time of admission were unremarkable. An abdominal ultrasound done a few days after admission did not show any lymphadenopathy or hepatosplenomegaly.

Hydroxychloroquine was stopped on admission because of concerns regarding agranulocytosis, and she was monitored for sepsis. After 24 h, was discharged home. The neutrophil count was noted to return to normal within days of stopping hydroxychloroquine. A diagnosis of hydroxychloroquine-induced agranulocytosis was made.

Discussion

Agranulocytosis is still considered a rare complication of treatment with hydroxychloroquine (2). A detailed literature search uncovered only a few past case reports detailing this particular side effect with hydroxychloroquine, and none gave the incidence for such an occurrence. However, other severe blood dyscrasias including leukopenia, aplastic anemia, and thrombocytopenia, have also been linked to hydroxychloroquine use (3). Mild leukopenia has been more frequently observed with cases of prolonged use of chloroquines, with one study giving an incidence of 4.8% (4). In the case reports found, all the patients appear to have been on hydroxychloroquine for several months before developing agranulocytosis, as in our case (2). In all cases, recovery from agran-

ulocytosis followed after the discontinuation of hydroxychloroquine.

The clinical findings in this case and investigations help support a diagnosis of drug-induced agranulocytosis. As mentioned, there was no evidence of sepsis, which is a known cause of the development of neutropenia in otherwise healthy patients, and viral studies were all negative. Although the patient in this case did not undergo bone marrow sampling, in other case studies where this was done, the sampled bone marrow was normal or only showed minor irregularities of white cell counts (2, 4). In the past, immune mechanisms have also been considered as a cause of this reaction. However, previous case studies have not found any evidence of pre-existing leukocyte autoantibodies, and Coombs tests were negative (5).

The total dose of hydroxychloroquine may be an important mechanism in the development of agranulocytosis (5). Hydroxychloroquine, like other 4-aminoquinolines (e.g., chloroquine), has a very high volume of distribution and has a slow renal clearance. Consequently, in chronic dosing, hydroxychloroquine has a substantial half-life, with current estimates being between 30 and 60 days, and it is well known to persist in the body for long periods (1, 2). For this reason, excessive plasma and tissue concentrations of hydroxychloroquine may have been a contributing factor in the development of agranulocytosis in this case.

One possibility that needs to be considered is the potential of rituximab to be involved either synergistically or an independent cause of agranulocytosis. Rituximab is a monoclonal antibody against CD20 that causes the lyses of B-lymphocytes (6). The synergistic effect of rituximab and hydroxychloroquine may have led to the patient developing agranulocytosis, but evidence for this remains to be seen in literature. Rituximab alone has been linked to blood dyscrasias. The increased use of rituximab has uncovered some new latent side effects, namely late-onset neutropenia (6). This is defined as grade III-IV neutropenia occurring 3–4 weeks

after treatment with rituximab. However, such cases are mostly seen in patients on treatment for various lymphomas and not in those with RA. In this case study, the patient had been given only two courses of rituximab, the last infusion being given over 6 weeks previously at the time of the development of agranulocytosis, which reduces the likelihood of rituximab involvement as a cause in this case.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.L.; Design - E.S.; Supervision - C.L.; Materials - H.P.; Data Collection and/or Processing - H.P., E.S.; Analysis and/or Interpretation - C.L., E.S., H.P.; Literature Review - H.P., E.S.; Writer - H.P., E.S.; Critical Review - E.S., C.L.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study has received no financial support.

References

1. Waller DG, Renwick AG, Hillier K. Medical Pharmacology and therapeutics. Second edition. Edinburgh: Elsevier Saunders; 2005.
2. Chernof D, Taylor KS. Hydroxychloroquine-induced agranulocytosis. Arch Dermatol 1968; 97: 163-4. [\[CrossRef\]](#)
3. Propp RP, Stillman JS. Agranulocytosis and hydroxychloroquine. N Engl J Med 1967; 277: 492-3. [\[CrossRef\]](#)
4. McDuffie FC. Bone marrow depression after drug therapy in patients with systemic lupus erythematosus. Ann Rheum Dis 1965; 24: 289-92. [\[CrossRef\]](#)
5. Neftel KA, Woodtly W, Schmid M, Frick PG, Fehr J. Amodiaquine induced agranulocytosis and liver damage. Br Med J (Clin Res Ed) 1986; 292: 721-3. [\[CrossRef\]](#)
6. Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine 2010; 89: 308-18. [\[CrossRef\]](#)