



Case report

Ofloxacin induced leucopenia in complicated falciparum malaria: a case report

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Abstract

Introduction: To report a case of ofloxacin-associated leucopenia, which occurred in a patient of falciparum malaria shortly after administration and resolved following discontinuation of the drug.

Case presentation: A 44 year old female was admitted in circulatory shock with a diagnosis of falciparum malaria, suffering from fever, diarrhoea and vomiting. After successful resuscitation she was treated with intravenous ofloxacin for Escherichia coli induced diarrhoea. She developed acute leucopenia that resolved after discontinuation of the drug.

Discussion: Ofloxacin is a broad-spectrum synthetic fluoroquinolone used for a wide variety of bacterial infections. Because of the temporal relationship between ofloxacin administration and the development of leucopenia in our patient, as well as the relationship between drug withdrawal and improvement in white blood cell count, ofloxacin-associated leucopenia was suspected. This reaction was categorized as probable according to the Naranjo probability scale. We report, for the first time in the English-language literature, a case of Ofloxacin-associated leucopenia. This association is further supported by the exclusion of other potential causes for this adverse effect.

Conclusion: Leucopenia is a well-recognized adverse effect of several drugs. We report a case of Ofloxacin-associated leucopenia during treatment of a patient with malaria. Healthcare personnel should be aware of this possible adverse reaction in patients treated with ofloxacin. A high degree of suspicion assumes special importance in this subgroup of critically ill patients with malaria where hematologic aberrations are common.

Introduction

Drug induced leucopenia may complicate any clinical situation. We present a case of probable ofloxacin induced leucopenia in a patient with falciparum malaria where the condition reverted to normal promptly after stopping the

drug. Cases of coexisting malaria and pancytopenia are not unknown in areas with a high prevalence of complicated falciparum malaria. A dilemma of deciding whether the leucopenia in a case of falciparum malaria is due to the disease process or an adverse drug reaction may arise at such times.

Case presentation

A 44-year Asian-Indian female presented with fever, diarrhoea and vomiting of five days duration. She was diagnosed to have *Plasmodium falciparum* malaria elsewhere by immuno-chromatographic test. Prior treatment received was parenteral artesunate for three days. A worsening clinical status necessitated referral to our institute for management.

At presentation, the patient was in circulatory shock - heart rate 160/min, blood pressure 80/50mmHg. She was resuscitated with intravenous fluids and inotropic agents. Biochemical examination showed raised serum urea (58 mg/dl), creatinine (2.1 mg/dl), liver enzymes and normal electrolytes (Sodium 138 meq/dl, Potassium 4.2 meq/dl). Hematological parameters included normal leukocyte counts ($8.6 \times 10^9/l$), mild anemia (Hemoglobin - 9.2 g/dl) and thrombocytopenia (platelets- $150 \times 10^9/l$) (Table 1). Bleeding and clotting times were normal. Chest x ray was normal.

Over the next two days signs of clinical deterioration suggestive of acute renal failure were noted. The patient continued to have severe diarrhoea. Alterations in haematological parameters showed worsening anemia (Hemoglobin -8 g/dl) and thrombocytopenia ($50 \times 10^9/l$). Total leukocyte counts were stable ($8.2 \times 10^9/l$). At this stage stool culture grew colonies of *Escherichia coli* which were sensitive to ofloxacin and carbapenem. The patient was started on intravenous ofloxacin (200 mg twice a day) after adjusting for impaired renal function.

After five days of treatment patient continued to deteriorate. She showed persistent oozing from site of puncture. Altered hematological profile included a drop in platelet counts, hemoglobin and packed cell volume. Severe leucopenia ($1.6 \times 10^9/l$) was noted.

Peripheral blood smear and quantitative buffy coat test for malaria parasite were negative. Erythrocyte sedimentation rate was 45, 55 and 50 mm in first hour and C reactive

protein of 65, 68 and 61 mg/dl on first, fourth and sixth days respectively. Chest X ray did not show any evidence of new infection. Ultrasonography of abdomen and pelvis was normal. Microbiological cultures from blood, tracheal secretions and urine failed to show any growth. Serial tests of sputum were negative for acid fast bacilli. Widal test was non reactive. On day six, hematologic profile continued to deteriorate (Table1).

Drug induced leucopenia was the provisional diagnosis. The patient was on injection ofloxacin, artesunate, pre and probiotics for diarrhoea, rabeprazole, salbutamol and dopamine infusion. Ofloxacin was discontinued at this stage.

Hematological profile showed signs of stabilization on day seven. The cell counts started improving (Table 1) and reached near normal levels by day ten of treatment. The patient had received no blood or component transfusion in the interim. Bone marrow done on day eight showed hypercellularity and signs of regeneration (Figure 1). Bone marrow differential counts revealed an increased promyelocyte (26%) and myelocyte count (18%). (Table 2)

She developed late-onset ventilator associated pneumonia by 18th day and was put on Carbapenem therapy. She stabilized with residual renal compromise requiring haemodialysis and was discharged after one month with complete recovery.

Discussion

Leucopenia in a critically ill patient can be attributed to various causes. Falciparum malaria is associated with anemia and thrombocytopenia due to hemophagocytosis and hemolysis. Leucopenia and pancytopenia are less common [1-3]. Lathia and colleagues have shown that thrombocytopenia alone (platelet count less than $150,000 \text{ mm}^{-3}$) was a predictor for malaria and in combination with anemia (Hb < 10 g/dl) it was next best parameter. RDW and leukocyte count were not

Table 1. Blood counts during the course of illness

DAY	Haemoglobin (g/dl)	TLC ($\times 10^9/l$)	DC (%)	Platelets ($\times 10^9/l$)	Reticulocyte (%)
Ofloxacin started on DAY 3					
Day 1	9.2	8.6	N57, E3, L39	150	0.3
DAY 3	10.0	8.2	N73, E2, L24	50	0.1
DAY 4	8.5	7.0	N72, E1, L25	50	0.1
DAY 5	7.3	1.6	N32, E6 L62	40	
Ofloxacin stopped on DAY 6					
DAY 6	10.2	1.5	N22, E6, L72	28	
DAY 7	10.3	2.7	N35, E2, L49	54	
DAY 9	9.6	10.0	N38, MMC2, MC9	81	5
Day 10	10.0	15.0	MC15/MC ₊ St6, E1, L32	150	6

Abbreviations: TLC: total leukocyte count; DC: differential count; N: neutrophils; E: eosinophils; L: lymphocytes; M: monocytes; MC: myelocytes; MMC: metamyelocyte; St: stab form.

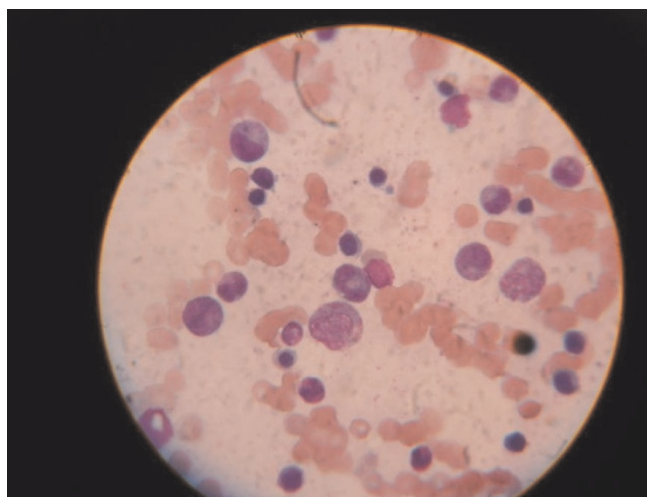


Figure 1. Bone marrow aspirate showing maturation arrest in the WBC series and erythroid hyperplasia. (leishman stain, ×100).

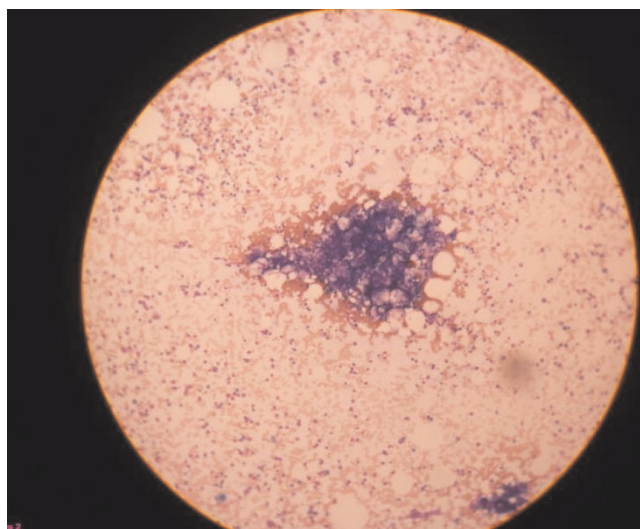


Figure 2. Bone marrow aspirate showing a marrow particle which is hypercellular. (leishman stain, ×10).

predictive [4]. Our patient had received a full course of antimalarial treatment and had no evidence for presence of parasites at the time of the episode of sudden leucopenia.

Other infections (tuberculosis, salmonellosis etc), sepsis and connective tissue diseases can cause macrophage activation syndrome [5] and leucopenia. Repeated smears showed absolute pancytopenia with no evidence of premature cells or hemolysis. Bone marrow biopsy did not reveal hemophagocytosis; splenomegaly was not documented. There was no evidence of severe sepsis in our patient in the form of rising CRP levels, or positive microbial cultures.

Drug-induced leukopenias can occur in a dose-dependent relationship or in an idiosyncratic, dose-independent hypersensitivity reaction. The antimalarial drug artesunate has proven to be very safe and the only incidents of

hematologic adverse effects associated with it occur when it is used in combination therapy [6] - with amodiaquine an agent known to cause leucopenia [7]. None of the other drugs being administered to our patient are known to cause this adverse effect. No drug other than Ofloxacin was discontinued prior to the rapid improvement in leucocyte counts.

Ofloxacin is a commonly used fluoroquinolone agent in gastrointestinal infections and been associated with adverse effects such as seizures, hypersensitivity vasculitis, hemoglobinurea etc [8,9].

Other drugs of this group have been implicated in serious hematologic adverse effects. Search of literature led us to similar cases where ciprofloxacin, levofloxacin, trovafloxacin and moxifloxacin were implicated as the cause of neutropenia, pancytopenia or bone marrow suppression [10-13]. The exact mechanism of action of these reactions are not well known till date. Having been administered for two days in a modified dose, serum level was not investigated. Re-challenge with the drug was not done due to ethical reasons.

The temporal sequence of events implicates ofloxacin as a probable cause of bone marrow suppression Naranjo probability scale score 6 [14] which exacerbated the pre-existing anaemia and thrombocytopenia. An idiosyncratic reaction cannot be ruled out.

Conclusion

Leucopenia in falciparum malaria is less common than anemia and thrombocytopenia.

Table 2. Bone marrow differential counts on eighth day

Cell type	Differential (%)	
	Case	Normal range (%)
Myeloblast	2	0.3-5.0
Promyelocyte	26	1-8
Myelocyte	18	8-16
Metamyelocyte + stab form	4	18-40
Segmented neutrophill	30	3-11
Eosinophil	1	1-5
Normoblast	18	18-36
Lymphocyte	17	11-23
Monocyte	1	0-0.8
Plasma cell	1	0.4-3.9
Myeloid:erythroid ratio	1.1	1.5-3.3

- Sudden onset leucopenia is more likely to be drug related.
- Ofloxacin may cause leucopenia as reported for other Quinolones.
- Suspected/most relevant drug possibly causing the leucopenia should be promptly stopped.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

ST was directly involved in patient management, decision making, conception and write up of the manuscript. AA was involved in the haematopathologic evaluation and assistance in manuscript editing.

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