Ofloxacin Induced Hemolysis in G6PD-deficient Patient: A Rare Cause of Pigment Nephropathy

Abstract
Thrombotic microangiopathy (TMA) commonly presents as a triad of acute kidney injury (AKI), jaundice, and hemolysis; however, tropical infections such as malaria, dengue, leptospira, and drugs like antimalarials can also have a similar presentation. They can cause AKI for many reasons including pre-renal causes but an important yet not relatively uncommon genetic cause of hemolytic anemia, that is, glucose 6-phosphate deficiency (G6PD) manifesting as jaundice, hemolysis, and AKI secondary to pigment nephropathy after receiving offending drugs needs to be worked up while evaluating such patients. Ofloxacin is not usually included in the lists of unsafe drugs in G6PD deficiency. Herein, we report a patient developing intravascular hemolysis secondary to G6PD deficiency associated with ofloxacin administration presenting as a rare cause for pigment nephropathy.

Keywords: G6PD deficiency, hemolysis, ofloxacin, pigment nephropathy

Introduction
Acute kidney injury (AKI), jaundice, and hemolysis in combination is a very common presentation of thrombotic microangiopathy (TMA); however, tropical infections such as malaria, dengue, leptospira, and drugs like antimalarial can also have a similar presentation causing AKI by many factors including prerenal causes but other important causes of hemolysis leading to pigment nephropathy. Important yet not relatively uncommon genetic predisposing factor of hemolytic anemia, that is, glucose 6-phosphate deficiency (G6PD) which can also manifest as jaundice, hemolysis, and AKI secondary to pigment nephropathy after receiving anti‑malarial drugs. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was discovered while investigating the development of hemolysis in patients who had received primaquine, and subsequently, several drugs have been linked to acute hemolysis in G6PD-deficient individuals.

It is often difficult to establish whether a specific drug directly causes a haemolytic crisis in G6PD-deficient patients. Hemolysis following ciprofloxacin therapy has been described; however, definitive evidence for such an association is still lacking. Hemolytic reactions to ofloxacin have been observed only in a few isolated cases and currently there are no published reports on an association between the two. Therefore, ofloxacin is not usually included in the lists of unsafe drugs in G6PD deficiency.

Case Report
A 24 years young male with no previous known comorbidities was admitted in a private hospital with a history of intermittent fever, abdominal pain, vomiting (non-bloody containing food particles), and decreased appetite for 4-5 days duration followed by decreased urine output for 2 days. On general examination at admission, the patient was dehydrated with a blood pressure of 100/60 mm Hg; heart rate was 110/min and the respiratory rate was normal. Body temperature was 36.8°C. White blood cell count was 24,200/µL, haemoglobin was 8.6 g/dL, platelets were 2.01 lacs and serum creatinine was 2.98 mg/dL. Symptomatic treatment was initiated with dicyclomine administered intravenously every 8 h, paracetamol injection for fever and when required and intravenous infusion of 5% glucose and normal saline solutions for re-hydration. Oral medications

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included ofloxacin 200 mg twice a day. However, there was no improvement and the lab reports showed downward trend in hemoglobin, worsening renal function and patient became completely anuric; hence referred to another hospital for further management.

On admission, he was anuric; vitals showed pulse of 108/mins, blood pressure of 130/70 mmHg in supine position and temperature of 37.9°C. Laboratory testing showed his hemoglobin of 4.1 g/dL, lactate dehydrogenase rose to 1503 U/L, total bilirubin was 2.62 mg/dL with indirect bilirubin of 1.47 mg/dL [Table 1]. Chest X-ray was normal and blood cultures were sent.

The patient’s previous medications including ofloxacin was discontinued and replaced with inj. Cefoperazone + sulbactum 1.5 gms twice daily, folic acid 5 mg once a day and 2 packed red cell transfusion was given. He was initiated on hemodialysis via right internal jugular double-lumen non-cuffed catheter in view of significant renal dysfunction and anuria. He was also given Inj. Methylprednisolone 500 mg daily for 3 days. Workup for hemolysis was initiated simultaneously and it revealed a reticulocyte count of 7.9%, peripheral smear showed anisopikilocytes but no schistocytes and Coomb’s test (indirect and direct) was negative. His urinalysis (urine being cola-colored) showed evidence of microscopic hematuria and proteinuria. Complement levels were low (C3-0.7 [normal range-0.9-1.8 g/L], C4- 0.09 [normal range-0.1-0.4 g/L]) and ANA profile was negative. His urinalysis showed +3 blood and protein with plenty of RBCs/HPF.

His G6PD levels were sent which came to be significantly low value of 2.1 despite evidence of ongoing hemolysis. We inquired about any other medication he might have received previously especially antimalarials; however, he denied, and all the bills of the medications didn’t reveal any other injections/oral tablets except that mentioned earlier. He required alternate day hemodialysis in view of persistent oligoanuria and 2 more packed cell transfusions. After 4 sessions of hemodialysis, he underwent left renal biopsy to know the cause of renal nonrecovery and to rule out immune complex-mediated glomerular pathology. Renal biopsy showed normal glomerular morphology with no evidence of intraglomerular or extra-capsillary hypercellularity. Tubules showed extensive dilatation and flattening of lining epithelium [Figure 1a] with red blood cell casts [Figure 1b]. Interstitium was mildly edematous and the blood vessels were largely unremarkable. Immunofluoroscence didn’t reveal any evidence of deposition of immunogloubulin. A diagnosis of acute tubular injury with pigment nephropathy was suggested.

He was continued on the same antibiotics for 10 days and then stopped in view of negative blood cultures and afebrile state. He was discharged on the 11th day with twice a week regular OPD follow up and hemodialysis was continued twice weekly till his urine output and renal function tests (monitored weekly) showed improvement. Gradually his urine output increased to 800–1000 mL/day and serum creatinine decreased to 4.4 mg/dL at which his hemodialysis was stopped, his hemoglobin remained stable at 9–10 g/dL requiring no further PCV transfusions, his steroids were also tapered serially by 10 mg/week and stopped at 4th week. He finally achieved s. creatinine of 1 mg/dL with

| Table 1: Lab parameters of our patient |
|--------------------------------------|
| Investigation | 03-Dec | 04-Dec | 05-Dec | 07-Dec | 12-Dec | 16-Dec | 07-Jan | 12-Jan | 17-Jan | 31-Jan |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Hb (g/dL)      | 8.6    | 5.8    | 4.1    | 5.2    | 9.3    | 8.3    | 10     | 11.4   | 12.4   | 12.3   |
| TLC (*1000/µL) | 24.2   | 16.7   | 12.2   | 12.8   | 11.7   | 12.3   | 12.4   | 11.6   | 9.3    | 9.5    |
| PLT (*1000/µL) | 201    | 175    | 167    | 152    | 193    | 302    | 212    | 234    | 270    | 272    |
| Reticulocyte Count (%) | 7.9 | 0.4 | 1503 | 612 | 150 |
| LDH (IU/L)     | 1180   | 102    | 69     | 30     |
| Blood urea (mg/dL) | 2.98 | 3.02 | 10.01 | 5.41 | 6.78 | 8.67 | 4.02 | 2.2 | 1.13 | 0.81 |
| S. creatinine (mg/dL) | 136 | 137 | 132 | 138 | 145 | 143 | 140 | 138 |
| S.Na+ (mEq/L)  | 4.19   | 4.25   | 3.8    | 4.3    | 4.4    | 3.7    | 3.5    | 3.8    | 4.2    | 3.6    |
good urine output of 2 l/d and hemoglobin of 12 g/dL at the 45th day of his illness. His repeat urinalysis also showed no evidence of microscopic hematuria and proteinuria. His complement levels normalized. He is being followed up on OPD basis now.

We had also sent his genetic analysis (G6PD gene sequencing by NGS) which revealed a homozygous missense variation in the exon 3 of G6PD gene (pAla74Gly) which has been classified as likely pathogenic-G6PD Orissa variant in tribal populations of India.

Discussion

The incidence of G6PD deficiency is highly variable in different parts of the world; however, in Indian population it varies between 0% and 10% and more so in tribal population. The case described in this report presented with severe hemolysis along with renal insufficiency. The precipitating cause appeared to be the administration of ofloxacin as no other drugs were given to the patient. Several drugs (analgesics, sulphonamides, anti-helminthics and antimalarials) have been known to precipitate hemolysis in G6PD-deficient patients. The proposed mechanism appears to be interaction of these drugs with hemoglobin and oxygen, leading to the formation of free oxygen radicals, which in GSH (reduced glutathione) depleted cells, further promotes oxidation of intracellular proteins and resulting in cell death. Apart from drugs, certain infections may also precipitate hemolysis in G6PD-deficient subjects which were however not evident in our case. Our patient showed signs of intravascular hemolysis in the form of raised LDH, bilirubin levels, and reticulocyte counts. Following this, complete workup for hemolytic anemia was undertaken which showed G6PD deficiency. These values hold no accuracy at the time of injury and may be normal; however, in our patient, despite the inciting mechanism existing he had low values confirming the diagnosis. Coombs tests were negative. Renal biopsy showed features of acute tubular injury with pigment deposition in tubules. Several studies have shown that various factors may contribute to renal injury following hemolysis, like blockage of renal tubules by hemolyzed red cells, intravascular coagulation leading to release of thromboplastin factors, decreased renal blood flow and glomerular filtration rate, or by a combination of these factors. In a study conducted by Choudhry et al. out of 20 G6PD-deficient children treated with drugs, 11 developed acute renal insufficiency and intravascular hemolysis, whereas 9 developed intravascular hemolysis alone.

The fluoroquinolones have become an increasingly popular class of antibiotics for use in a variety of infections, with ciprofloxacin probably being most frequently marketed and prescribed in the past. The WHO working group 1989 doesn’t mention fluoroquinolones as unsafe in G6PD deficiency however, Harrison’s internal medicine 20th edition mentions ciprofloxacin and norfloxacin to be in a possible risk category for G6PD deficient. Some studies mention Ofloxacin to be safe in G6PDH deficiency; however, the British National Formulary Sept 2010 mentions ofloxacin and moxifloxacin in the definite risk category of hemolysis for G6PD-deficient candidates. Hemolytic anemia is listed among adverse reactions at low frequencies (less than 1%), however, not consistently associated with G6PD deficiency (e.g., norfloxacin, ciprofloxacin). Ciprofloxacin is classified as being unsafe in G6PD deficiency by the “Italian Favism-G6PD Deficiency Association” in the Mediterranean region and Asia; however, hemolytic reactions to ofloxacin have been reported only in few unpublished cases. As per our knowledge, this case is 1st to be reported in the literature.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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