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Hemolysis Supported by Levofloxacin in an SS Sickle Cell Patient

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Abstract

The occurrence of acute hemolysis in a patient with stable hemoglobinosis can be of corpuscular or extra-corpuscular origin. We report the case of a patient with sickle cell disease SS stable for twenty years, who is treated with levofloxacin for sepsis with a urinary starting point. Biology: hyperleukocytosis at 33,570/mm^3 made up of 90% neutrophils and CRP at 160 mg/l, hemolytic, mechanical, nonthrombocytic microcytic anemia (Hb at 8.3 g/dl, VGM at 70 µm^3, haptoglobulin collapsed < 0.1, weakly positive schistocytes < 0.1%, PL at 277,000 with no evidence for DIC, the fibrinogen level is rather high at 5.68 g/l and hemostasis is normal. blood ionogram, renal function is normal with blood urea at 4 mmol/l and creatinine at 62 µmol/l. The rest of the blood ionogram are normal apart from the proteins which are contracted at 93 g/l. The liver test shows a Bilirubin total at 144 UI/L, Conjugated bilirubin at 38 UI/L, Free Bilirubin at 106 UI/L, PAL at 166, ASAT and ALAT at 50 UI/L, GGT, Amylase are normal. The iron balance is rather inflammatory with low serum iron at 8 µmol/l, saturation at 13% and high serum ferritin at 462 µg/l ECBU comes back positive for entero bacter chloacae with significant leukocyturia at more than 100,000/ml associated with hematuria at 25,000/ml complicated by bacteremia with the same germ. The evolution is marked by the persistence of haemolytic signs despite the regression of inflammatory markers. Levlofloxacin unmasks a G6PD deficiency. The substitution of levolofloxacin by cefixime allows a clear clinical and biological improvement.

Subject Areas

Hematology, Pharmacology

Keywords

Hemolysis, Sickle Cell Disease, G6PHD, Levofloxacin, Prostatitis

1. Introduction

Sickle cell disease is an autosomal disease characterized by a mutation at the 6th codon of the beta chain of hemoglobin, GAG being replaced by GTG. G-6-PD is an enzyme of anaerobic glycolysis which only participates for 10% in the production of the energy necessary for the red blood cell, but which remains the key enzyme for the regeneration of reduced glutathione, essential for the protection of the red blood cell against oxidation [1]. Drug-induced immune hemolytic anemia is extremely rare.

Medications such as methyldopa, fludarabine, and procainamide have traditionally been associated with autoimmune hemolytic anemia. Fluoroquinolones such as temeloxacin, pefloxacin and ciprofloxacin have been associated with severe hemolysis [2].

We report the case of a patient with sickle cell SS stable for twenty years, who is treated with levofloxacin for sepsis with a urinary starting point.

It is important for clinicians to recognize this rare complication caused by a commonly prescribed medication, levofloxacin.

2. Case Report

A 41-year-old, from the Democratic Republic of Congo is known to be a carrier of homozygous sickle cell disease diagnosed in childhood, polytransfused, the last of which dates back to 1978. His only notable history is a cholecystectomy in 2001. His vaccination against-pneumococcal and anti-hepatitis B is not up to date.

He presents to the emergency room with diffuse abdominal pain without defense or contracture associated with dysuria, nausea and vomiting without transit disorder. On clinical examination, the patient is febrile at 38˚C, hemodynamically stable at 112/69 mmHg without tachycardia. The lumbar fossae are free and painless, rectal examination is painful. The testicles are painless and the hernial orifices are free. The urine dipstick is positive for leukocytes, nitrites and red blood cells. The rest of the clinical examination shows conjunctival jaundice; a dehydrated patient without signs evoking a meningeal syndrome or a surgical abdomen. Acute prostatitis is suspected and the patient is immediately put on Levlofloxacin 500 mg per day and gentamicin 120 mg in single-dose infusion for three days.

Complementary examinations on admission found a significant biological inflammatory syndrome, hyperleukocytosis at 33,570/mm^3 made of polymorphonuclear neutrophils at 90% and a CRP at 160 mg/l, hemolytic, mechanical, non-thrombocytic microcytic anemia (an Hb at 8.3 g/dl, a VGM at 70 µm^3, a collapsed haptoglobulin < 0.1, weakly positive schistocytes < 0.1%; PL at 277,000 without evidence for DIC, the fibrinogen level is rather high at 5.68 g/l and haemostasis is normal On the blood ionogram, renal function is normal with blood urea at 4 mmol/l and creatinine at 62 µmol/l. The rest of the blood ionogram are normal apart from proteins which are contracted at 93 g/l. The liver test shows a Bilirubin total at 144 Umol/l, Conjugated bilirubin at 38 Umol/l, Free bilirubin at 106 Umol/l, PAL at 166, GOT and GPT at 50 UI/L, GGT, Amylase are normal. The iron balance is rather inflammatory with a low serum iron at 8 µmol/l, saturation at 13% and a high ferritin level at 462 µg/l. The CBEU comes back positive for enterobacter chloacae with a significant leucocyturia at more than 100,000/ml associated with hematuria at 25,000/ml complicated by bacteraemia from the same germ. ECG and chest X-ray are normal. Abdominal and prostate ultrasound showed the presence of a small heterogeneous plaque in the left lobe of the prostate, compatible with a focus of acute prostatitis without signs of abscess.

The clinical and biological evolution in terms of infection is rather favorable under antibiotics with total apyrexia on day 2 and regression of the biological inflammatory syndrome with a CRP at discharge of 47 mg/l. The control CBEU is sterile. The stability of the infectious picture contrasts with the persistence of homeless with a drop in the hemoglobin level to 7 g/l, a haptoglobin which always remains collapsed < 0.1. Platelets and LDH are normal, *i.e.* 411,000/mm^3 and 362 respectively. Control hepatic assessment shows, in addition to the initial persistent cholestasis, moderate hepatic cytolysis with GOT at 73 UI/L and GPT at 61 UI/L. The Coomb's test, the search for anti-IgG and anti-C3 antibodies remain negative. The rest of the biological assessment is within normal limits.

At day, while the patient is on levofloxacin 1000 mg per day orally; he develops intense osteo-articular and abdominal pain with slowing of intestinal transit and pain in the lumbar fossae without functional urinary signs or hematuria. Radiological and ultrasound exploration is non-contributory. This clinical picture evokes a vaso-occlusive crisis treated symptomatically by parenteral hydration, oxygen therapy, transfusion of 2 red blood cells and a combination of morphine and nefopam analgesics. Given the persistence of hemolysis despite the control of sepsis and the vaso-occlusive crisis of sickle cell disease, a drug cause was suspected. Levofloxacin is substituted by cefixime. Its cessation was followed by the gradual and complete disappearance of haemolysis.

A G6PD deficiency in homozygous SS sickle cell disease contraindicating the use of levofloxacin is suspected. An enzymatic assay of G6PD is performed revealing a level of 56 mIU for a normal greater than 80 mIU, indicating a deficit with a moderate to severe haemolytic risk. The deficiency being linked to homozygous SS sickle cell disease.

3. Discussion

This observation draws attention to the possibility of maintaining intravascular hemolysis by infectious and pharmacological agents. When the infection seems to be under control and the patient becomes afebrile; he continued to show signs of hemolysis suspected to be secondary to continued treatment with levofloxacin. The latter has been described to induce hemolysis by an autoimmune mechanism or secondary to a G6PD deficiency; common mechanism with all fluoroquinolones [2] [3]. In our study, the Coombs test was negative.

Levlofloxacin unmasks a G6PD deficiency causing hemolysis in a perfectly stable SS sickle cell patient. The cessation of this was followed by the complete disappearance of hemolysis. We did not need any other specific treatment for this haemolysis.

Sickle cell disease and G-6-PD deficiency are genetic abnormalities of the red blood cell responsible for hemolytic anemia. The association of these two anomalies in the same patient deserves to be recognized in order to better adapt the management.

The sequence of events and the clinical presentation are highly suggestive of hemolysis induced by the G-6-PD deficiency unmasked by levofloxacin. This association should be suspected in any patient presenting with signs of haemolysis of undetermined origin where this enzymopathy is widespread; this is the case in subjects of Mediterranean or African origin [1].

Our patient's clinical signs and symptoms, as well as laboratory findings, are consistent with the clinical presentation of hemolysis: a significant decrease in hemoglobin and haptoglobulin, large increases in LDH, elevated bilirubin unconjugated and the presence of schistocytes. The association of an increase in serum LDH and a decrease in haptoglobin is 90% specific for the diagnosis of hemolysis.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common congenital enzyme deficiency worldwide. About 400 million people are affected, with varying clinical manifestations. Due to globalization, migratory behavior and travel habits, it is also increasingly common to observe cases of G6PD deficiency in Europe. The enzyme deficiency is transmitted in a recessive hereditary mode linked to the X chromosome. In sub-Saharan Africa, the G6PD A variant is the most frequent [4]. In West and Central Africa 10% to 15% of the population are affected; a similar prevalence is found among African Americans. Caucasians predominantly present with the Mediterranean G6PD variant, with increased frequency in coastal Sardinia and Greece (20% - 35%), as well as in the Middle East (Kurdish Jews 60% - 70%).

4. Conclusion

Levofloxacin unmasks a G6PD deficiency causing hemolysis in a patient with homozygous sickle cell disease. The immediate discontinuation of the incriminated drug made it possible to stop the mechanism. Levofloxacin-induced he-

molytic anemia is a serious and rare complication. This side effect should be known by clinicians especially in case of G6PDH deficiency.

Conflicts of Interest

The authors declare no conflicts of interest.

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