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Case Report

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Acute Hemolytic Anemia Induced by Levofloxacin in a Woman With G6PD Deficiency: A Case Report

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ABSTRACT

Introduction: Glucose 6-Phosphate Dehydrogenase deficiency (G6PD) is an X-linked recessive disorder recognized as the most prevalent enzyme deficiency around the world. G6PD deficiency has a high prevalence in Iran, especially in the northern regions. As we know, hemolysis in G6PD patients was not reported with levofloxacin previously.

Case Report: In this report, we introduce a 54-year-old G6PD deficient woman who experienced the symptoms of hemolytic anemia following completion of treatment with levofloxacin.

Result: After ruling out other causes of hemolysis, by using the Naranjo scale, levofloxacin was considered as a possible cause of hemolysis.

Conclusion: Though the hemolytic anemia induced by levofloxacin is extremely rare in G6PD deficient patients, drug-induced hemolytic anemia should be considered as one of the differential diagnoses. It would be appropriate to use an alternative antibiotic instead of levofloxacin in a G6PD deficient patient.

Introduction

Glucose 6-Phosphate Dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in the world, with about 400 million people affected. This is an X-linked recessive disorder, so it is expected to occur predominantly in men [1]. This disorder is observed in women when both X chromosomes have no related gene or have been mutated [2]. Although the enzyme is expressed in all tissues, its major clinical complications are related to red blood cells. Human red blood cells require the oxidative

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pathway of the pentose phosphate cycle to maintain cell integrity and function [3].

Most people with G6PD deficiency under normal conditions are completely asymptomatic and the symptoms occur only when exposed to oxidative stress. Major clinical complications of this enzyme disorder include chronic non-spherocytic hemolytic anemia, neonatal jaundice, and acute infectious hemolytic anemia such as bacterial infections like Salmonella, Escherichia, beta-hemolytic Streptococcus, Rickettsia, and viral infections, as well as infectious hepatitis, pneumonia, and typhoid fever. The consumption broad bean and some medications (including sulfonamide-based drugs, antibiotics such as nitrofurans and antimalarial drugs such as primaquine and chloroquine) also contribute to hemolysis in these patients [4, 5]. Problems such as the false negative of diagnostic tests in the acute phase and the heterozygosity of female patients make the G6PD deficiency difficult to detect [6, 7].

It is often difficult to prove that a particular drug directly causes a hemolytic crisis in patients with G6PD deficiency. Levofloxacin-induced hemolytic reactions have been only reported in a few cases, such that resulting hemolysis occur as autoimmune reactions and renders the Coombs test to be positive [7]. Hence, the fluoroquinolones are not usually included in the unsafe list of G6PD deficiency [8]. According to the World Health Organization, G6PD deficiency is observed in Iran among 10% to 14.9% of the population. The G6PD deficiency, especially in Mazandaran province, has a high prevalence [9]. In this study, a case of acute hemolytic anemia induced by levofloxacin is reported in a patient with the G6PD-Mediterranean deficiency.

Case Presentation

The patient was a 54-year-old woman with a dry cough and epigastric pain disseminated to the periumbilical area and upper quadrant of the abdomen improving by sitting and getting worse by lying, who was admitted to the Imam Khomeini educational Hospital in Sari, North of Iran. In the examinations, the patient was conscious with blood pressure 130/70 mmHg, heart rate 110 beats per minute, respiratory rate 18 breaths per minute, and temperature 38°C. Abdominal and pelvic ultrasound was normal. The patient had a history of hypertension and diabetes which were controlled by drug therapy including atenolol, regular and NPH insulin. The baseline tests were as following: Red Blood Cell (RBC) 3.3 million cells/µL; Hemoglobin (Hb) 10.4 g/dl; Mean Cell Volume (MCV) 97.6 fl; Mean Cell Hemoglobin (MCH) 31.5 pg; White Blood Cells (WBC) 17400 cell/µL; Platelet (Plt) 311000 /µL; Creatinine (Cr) 1 mg/dl; Urea 27 mg/dl; direct bilirubin 0.2 mg/dl; troponin: negative. According to the hematology results, the patient indicated normocytic normochromic anemia.

Normal saline, pantoprazole 40 mg slow Intravenous (IV), ranitidine 50 mg slow IV TDS, ceftriaxone 1g BD and ciprofloxacin IV 400 mg stat over 1 hour were initially administered. Also, to Complete Blood Count (CBC), the serum ferritin levels were requested to be tested in assessing the cause of anemia. The serum ferritin level (582 ng/ml) in the patient was higher than the normal range in women (10-120 ng/ml). Two days after hospitalization, she was diagnosed with empyema and right lower lobe lung abscess based on CT scan findings. On the third day of admission, the foul-smelling exudative pleural effusion was removed from her right lung. On the third day of hospitalization, due to the common cause of empyema (anaerobic bacteria) and the patient's clinical findings (smelly fluid), her antibiotics were switched to ceftriaxone (1 g IV daily), clindamycin (600 mg IV daily) and levofloxacin (500 mg PO daily). Additionally, Total Iron Binding Capacity (TIBC) of the patient was 200 µg/dl and her serum iron level was 13 µg/dl. On the seventh day of hospitalization, she was icteric and transferred to the Intensive Care Unit (ICU) because of acute tachypnea, icterus, fever, and hematuria. All medications received by the patient were discontinued and she received two packed cell units due to high hemoglobin loss (4 g/dl).

To detect the cause of hemolysis, a direct Coombs test was requested. The test result was negative. Moreover, the blood lead level was requested due to the addiction of the patient to opium. High blood levels of lead (49µg/dl) suggested lead poisoning. During the admission of the patient to the ICU, the daughter of the patient stated that the patient suffered from G6PD deficiency. After stabilizing the condition of the patient, tablet folic acid 5mg daily was started. It was not appropriate to measure the G6PD enzyme level due to hemolysis. Due to G6PD deficiency and using the Naranjo scale [10], the cause of hemolysis in patients was considered to be levofloxacin (7 score, probable adverse drug reaction).

The laboratory findings of patient are presented in Table 1. After the discontinuation of treatment with levofloxacin and the onset of supportive treatment, the patient was transferred to the ward after three days. She was hospitalized for 31 days for management of her exudative pleural effusion and reduction of the lung sounds in the right lower lobe with the insertion of the chest tube

and drainage of the exudative pleural effusion. Finally, she was discharged with the drug order of tablet cefixime 400mg daily, tablet folic acid 5 mg daily, and capsule clindamycin 300 TDS with a good general condition.

Discussion

To the best of our knowledge, this is the first case of levofloxacin-induced hemolysis in a patient with G6PD deficiency. Despite the high lead level in the patient that indicates lead poisoning, laboratory findings (low level

Table 1. Laboratory findings of the patient

	Clinical Course								
Test (Normal Range)	**Day 1 (ED)**	**Day 3 Hospital**	**Day 4 Hospital**	**Day 5 Hospital**	**Day 8 Hospital**	**Day 9 Hospital**	**Day 12 Hospital**	**Day 13 Hospital**	**Day 29 Hospital**
Hemoglobin (12.0-15.5 g/dL)	10.4	10.4	9	-	4.1	4	8.8	8.4	8
Hematocrit (36-48%.)	32.2	28.4	26.6		11.9	12.3	28.6	28.6	26.8
MCV (80-99 fl)	97.6	97	97	-	97	98	97	102	100
MCH (27-35 Pg)	31.5	32	33	-	35	32	30	30.2	29.9
MCHC (27-35 g/dL)	32	33	34	-	34	33	32	29.5	-
RDW-CV (10.6-15.7%)	12.7	13.1	15.4	-	19.4	19.4	15.9	20	17
Fe 60-180 µg/dL	-	13	-	-	-		41	-	-
Ferritin (10-120 ng/mL)	-	-	582	-	-		767	-	-
TIBC (220-420 ng/dL)	-	200	-	-	-		225		-
RBC 4.2 to 5.4 million cells/µL	3.3	2.97	2.74	-	1.22	1.25	2.78	2.94	2.68
WBC (4.5 to 11.0×109/L)	17.4	20.7	22	-	13.4	11.9	12.1	6.5	-
Corrected reticulocyte(0.5%-1.5%.)							4.6	4.4	-
Reticulocyte(0.5%-1.5%.)							7.2	7	-
LDH (140 U/L - 280 U/L)	-	-	-	-	825		950	670	-
Lead blood level (≤25µg/dl)	-	-	-	-	-	-	-	49	-
Unconjugated bilirubin (≤0.3 mg/dL)	0.2	0.2	-	-	1.1		0.4	-	-
Urine urobilinogen (0.2 EU/dL)	negative	-	-	-	-		-	-	-
Urine bilirubin (negative)	negative	-	-	-	-		-	-	-
Direct antiglobulin test (direct Coombs') (negative)	-	-	-	-	-	negative	-	-	-
SCr (0.6–1.3 mg/dL)	1	-	-	0.9	1.9		0.9	0.9	1

MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW-CV: Red Blood Cell Distribution Width; TIBC: Total Iron Binding Capacity; RBC: Red Blood Cell; WBC: White Blood Cell count; LDH: Lactate Dehydrogenase; SCr: Serum Creatinine

of iron and high level of ferritin), and clinical evidence of the patient (absence of neurological symptoms) did not support lead-induced hemolysis. Regarding the negative results of the direct Coombs test, autoimmune hemolytic anemia was also ruled out. Hemolytic anemia can be inherited or acquired. The most common cause of acquired hemolytic anemia is autoimmune reactions [11]. The negative result of direct coombs test in this patient rules out the hemolytic anemia caused by autoimmune reactions. One of the hereditary causes of hemolytic anemia is G6PD deficiency [12]. The cause of hemolysis was considered to be the use of levofloxacin according to the score obtained from the Naranjo Scale, within the probable ADR range [10], and the presence of underlying G6PD deficiency [10]. Fluoroquinolones are a popular category of antibiotics that are used for various infections [13]. Youngster et al. during an evidence-based systematic review stated that there were inadequate documents for hemolysis in normal doses of fluoroquinolones [14]. However, a review study opposes this finding and recommends that even a case report of adverse effects should be taken seriously [5]. Besides, there are convincing reports to support the avoidance of quinolones in patients with G6PD [15, 16]. It seems that the safety issues of fluoroquinolones in G6PD deficiency require further research.

Opposite to levofloxacin-induced autoimmune hemolytic anemia, hemolysis in G6PD deficiency setting following the use of levofloxacin has not been reported yet. Levofloxacin-induced hemolysis driven by an autoimmune mechanism can be delayed even after the completion of the treatment course [7].

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information. They were free to leave the study whenever they wished, and if desired, the research results would be available to them. Written consent has been obtained from the subjects. Principles of the Helsinki Convention were also observed.

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Conflict of interest

The authors declared no conflict of interest.

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References

[1] Parsanathan R, Jain SK. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is linked with cardiovascular disease. Hypertension Research. 2020; 43(6):582-4. [DOI:10.1038/s41440-020-0402-8] [PMID]

[2] Domingo GJ, Advani N, Satyagraha AW, Sibley CH, Rowley E, Kalnoky M, et al. Addressing the gender-knowledge gap in glucose-6-phosphate dehydrogenase deficiency: Challenges and opportunities. International Health. 2019; 11(1):7-14. [DOI:10.1093/inthealth/ihy060] [PMID] [PMCID]

[3] D'Alessandro A, Fu X, Kanias T, Reisz JA, Culp-Hill R, Guo Y, et al. Donor sex, age and ethnicity impact stored red blood cell antioxidant metabolism through mechanisms in part explained by glucose 6-phosphate dehydrogenase levels and activity. Haematologica. 2020; 106(5):1290-1302. [DOI:10.3324/haematol.2020.246603] [PMID] [PMCID]

[4] Chan TK, Chesterman CN, McFadzean AJ, Todd D. The survival of glucose-6-phosphate dehydrogenase-deficient erythrocytes in patients with typhoid fever on chloramphenicol therapy. The Journal of Laboratory and Clinical Medicine. 1971; 77(2):177-84. [PMID]

[5] Luzzatto L, Seneca E. G6PD deficiency: A classic example of pharmacogenetics with on-going clinical implications. British Journal of Haematology. 2014; 164(4):469-80. [DOI:10.1111/bjh.12665] [PMID] [PMCID]

[6] Jamwal M, Sharma P, Das R. Laboratory approach to hemolytic anemia. The Indian Journal of Pediatrics. 2020; 87(1):66-74. [DOI:10.1007/s12098-019-03119-8] [PMID]

[7] Oh YR, Carr-Lopez SM, Probasco JM, Crawley PG. Levofloxacin-induced autoimmune hemolytic anemia. Annals of Pharmacotherapy. 2003; 37(7-8):1010-3. [DOI:10.1345/aph.1C525] [PMID]

[8] Glader B. Diagnosis and management of Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency [Internet]. 2019 [Updated 2021 March 17]. Available from: https://www.uptodate.com/contents/diagnosis-and-management-of-glucose-6-phosphate-dehydrogenase-g6pd-deficiency

[9] Mesbah-Namin SA, Sanati MH, Mowjoodi A, Mason PJ, Vulliamy TJ, Noori-Daloii MR. Three major glucose-6-phosphate dehydrogenase-deficient polymorphic variants identified in Mazandaran state of Iran. British Journal of Haematology. 2002; 117(3):763-4. [DOI:10.1046/j.1365-2141.2002.03483.x] [PMID]

[10] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1981; 30(2):239-45. [DOI:10.1038/clpt.1981.154] [PMID]

[11] Dhaliwal G, Cornett PA, Tierney Jr LM. Hemolytic anemia. American Family Physician. 2004; 69(11):2599-606. [PMID]

[12] Frank JE. Diagnosis and management of G6PD deficiency. American Family Physician. 2005; 72(7):1277-82. [PMID]

[13] Suaifan GARY, Mohammed AAM. Fluoroquinolones structural and medicinal developments (2013-2018): Where are we now? Bioorganic & Medicinal Chemistry. 2019; 27(14):3005-60. [DOI:10.1016/j.bmc.2019.05.038] [PMID]

[14] Youngster I, Arcavi L, Schechmaster R, Akayzen Y, Popliski H, Shimonov J, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: An evidence-based review. Drug Safety. 2010; 33(9):713-26. [DOI:10.2165/11536520-000000000-00000] [PMID]

[15] Sansone S, Rottensteiner J, Stocker J, Rosanelli C, Wiedermann CJ. Ciprofloxacin-induced acute haemolytic anaemia in a patient with glucose-6-phosphate dehydrogenase Mediterranean deficiency: A case report. Annals of Hematology. 2010; 89(9):935-7. [DOI:10.1007/s00277-010-0903-7] [PMID]

[16] López PC, García LL, Ruiz JM, Fernández EM, López PC. Anemia hemolítica aguda por Ciprofloxacino. Revista de Medicina de Familia. 2016; 20(22):1-3. https://www.revistafml.es/upload/ficheros/noticias/201608/caso_clinico__anemia_hemolitica.pdf