CASE REPORT

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DIAGNOSIS OF RARE SC HEMOGLOBINOPATHY AFTER ANTIBIOTIC THERAPY IN A HOSPITAL SETTING: CASE REPORT

DIAGNÓSTICO DE HEMOGLOBINOPATIA RARA SC APÓS ANTIBIÓTICOTERAPIA EM AMBIENTE HOSPITALAR: RELATO DE CASO

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ABSTRACT

SC Hemoglobinopathy is the result of heterozygous inheritance of the HbS and HbC alleles and can be the cause of anemic episodes. Under certain circumstances, the use of drugs may induce anemia as in membranopathies, erythroenzymopathies or in hemoglobinopathies. The present study reports the case of a 52 year old patient with infection at a surgical site after cervical arthrodesis following a C6 cervical spine fracture. The patient developed severe anemia (hemoglobin 5.8 g/dL) after administration of vancomycin and cefepime. After high performance liquid chromatography, it was elucidated that the patient was a carrier of hemoglobin SC. The use of antimicrobials showed a correlation with anemia, indicating the relevance of the rational use of drugs and the appropriate correlation between clinical and test results, especially in hospital settings.

KEYWORDS: Anemia; Antibiotics; Hemogloginopathies; Hemoglobin SC.

RESUMO

A hemoglobinopatia SC é resultado da herança heterozigótica dos alelos HbS e HbC e pode ser a causa de episódios anêmicos. O uso de medicamentos pode, em determinadas circunstâncias, induzir anemias como em membranopatias, eritroenzimopatias ou em hemoglobinopatias. O presente estudo relata o caso de um paciente de 52 anos, com infecção em sítio cirúrgico após a realização de artrodese cervical decorrente de uma fratura na coluna cervical em C6. Houve, no curso evolutivo, quadro de anemia severa (hemoglobina de 5,8 g/dL) após após a administração de vancomicina e cefepime. Após a realização de cromatografia líquida de alta performance foi elucidado tratar-se de paciente portador de hemoglobina SC. O uso de antimicrobianos demostrou correlação com o quadro anêmico o que indica a relevância do uso racional de medicamentos e da correlação adequada entre a clínica e os exames realizados, sobretudo em ambiente hospitalar.

DESCRITORES: Anemia; Antibióticos; Hemogloginopatias; Hemoglobina SC.

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INTRODUCTION

Normal adult hemoglobin is a heterotetramer consisting of two pairs of globin polypeptide chains, one pair of alpha chains and another pair of non-alpha chains, namely: beta (HbA), delta (HbA2), and gamma (HbF) chains. These polypeptide chains are folded such that the four heme groups invade the molecule to form the structure of hemoglobin.[1]

While hemoglobinopathy C results from a mutation that leads to the amino acid substitution of glutamic acid by a lysine in the sixth position of the beta-globin chain, hemoglobin S results from a mutation that involves the amino acid substitution of glutamic acid by neutral valine in the sixth position of the beta-globin chain.[1,2]

Thus, hemoglobinopathy SC occurs when the sickle cell gene is co-herited with the mutant hemoglobin C gene, and results from heterozygous inheritance of the HbS and HbC alleles. The disease is considered a mild form of sickle cell disease. More people throughout the world have hemoglobinopathy SC than sickle cell disease or sickle cell anemia itself, resulting from the SS genotype.[3-5]

West Africa is home to the largest population of individuals with HbSC disease. Worldwide, 55,000 children are born with HbSC disease each year. In the United States and the United Kingdom, HbSC accounts for 25% to 30% of sickle cell disorders.[2,3]

Sickle cell disease confers a 30-fold increase in the risk of sepsis due to functional asplenia or splenic ischemia resulting from sickling.[3,4] Pain crises in children with hemoglobinopathy SC occur half as frequently as in sickle cell anemia.[5]

Since this hemoglobinopathy is rare and can be harmful to the patient's health, analytical methods such as hemoglobin electrophoresis and high-performance liquid chromatography (HPLC) are of utmost importance and most commonly used. Patients heterozygous for hemoglobin C disease may have 30% to 40% HbC, 50% to 60% HbA, and increased HbA2.(1) In this study, a case report of a hemoglobin SC carrier patient with hemolytic anemia resulting from antibacterial drug use is presented. The research was approved by the Ethics Committee of the Federal University of Piaui under CAAE n° 01812918.3.0000.5214, opinion number 5.625.649.

CASE REPORT

A 52-year-old male patient, smoker, alcoholic, with no comorbidity and no history of allergies, was admitted to the Tibério Nunes Regional Hospital, Floriano-Piauí, in February 2022 with a history of a fall from a staircase on January 21, 2022, evolving with cervicalgia and dysphagia. After medical evaluation, a fracture was found in the spine, in the cervical region at C6/C7 vertebrae. Thus, the patient was transferred to the University Hospital of the Federal University of Piauí (HUPI), Teresina-Piauí, and was admitted on January 25, 2022.

He underwent cervical arthrodesis surgery on February 1, 2022. At that time laboratory test alterations indicated leukocytosis (WBC: 24,000/mm3) with neutrophilia (neutrophils: 23,200/mm3), lymphopenia with atypical lymphocytes, toxic granulations and elevated C-reactive protein (CRP) (26.7 mg/L). The total bilirubin level slightly increased (1.39 mg/dL) with 0.52 mg/dL direct bilirubin and 0.88 mg/dL indirect bilirubin. In view of these findings, he was placed on cefuroxime antibiotic therapy from February 1 to February 4 (750 mg, IV-EV, every 8 hours). The blood count also showed a hemoglobin of 9.6 g/dL with normal hematometric indices, i.e., the presence of normocytic and normochromic anemia.

Three days after cefuroxime administration the patient had a fever (38.2°C) and serosanguinous secretion in the surgical wound (SW). After that, antibiotic therapy was started with the association of cefepime (1g, IV, 8/8 h) and vancomycin (1g, IV, 12/12 h) for 7 days. After this treatment regimen, leukometry was 7,520/mm3 and CRP levels were 20.4 mg/L. Anemia

worsened (Hb = 5.8 g/dL) and the patient showed anisocytosis with microcytes. Due to the maintenance of abundant secretion from the SW, antibiotic therapy was extended for 21 days, followed by SW dehiscence with exposure of the spinous processes. In the meantime, the patient exhibited important hematological alterations with the presence of circulating poikilocytes (codocytes and dacryocytes).

On March 4, 2022, a new extensive proceding was performed to clean the SW with treatment of liquoric fistula. On March 09, 2022, according to a consultation carried out by the Hospital Infection Control Committee (CCIH), the patient was advised to stop the instituted antibiotic therapy, which was replaced with the association of sulfamethoxazole 400 mg with trimethroprime 80 mg, orally, 12/12h, for 7 days along with tigecycline 50 mg IV 12/12h. Subsequently, the patient demonstrated a good general condition, with a dry SW and clinical improvement although his last blood count on March 21, 2022, indicated severe anisopoikilocytosis with maintaining the presence of codocytes and now also with drepanocytes, which prompted an investigation for variant hemoglobins. High performance liquid chromatography (HPLC) of hemoglobin revealed 56% HbS, 29.7% HbC, 4.1% HbF, 5.1% HbA2 and 5.0% Hb A.

DISCUSSION

This report shows the complexity of the diagnosis of hemolytic anemias and the importance of clinically recognizing such a situation. The patient already showed a mild normocytic and normochromic anemia upon admission that intensified after initiation of antibiotic therapy due to a hospital-acquired infection after cervical arthrodesis. In view of this, laboratory test showed a reactive blood count with leukocytosis at the expense of neutrophilia and increased CRP. Table 1 shows the patient's laboratory test alterations during the course of hospitalization.

Tabela 1 - Parâmetros laboratoriais observados no curso da internação hospitalar.

Parameter	26/01	01/02	05/02	15/02	23/02	08/03	12/03	21/03
Red blood cells (10^6/mm^3)	3.44	3.1	3.24	2.09	3.37	3.13	3.43	3.43
Hematocrit (%)	29.6	26.3	27.6	17.5	27.5	24.6	27	26.6
Hemoglogin (g/dL)	10.7	9.6	10	5.8	9.4	8.6	9.5	9.8
VCM (fL)	86	84.8	84.6	85.2	83.7	81.6	78.7	78.1
HCM (pg)	31.1	31	30.9	27.8	27.9	27.5	27.7	28.6
MCHC (g/dL)	36.1	36.5	36.2	33.1	34.2	35	35.2	36.6
RDW (%)	13.1	13	13.2	15.7	17	17.2	16.2	19.3
Leukocytes (/mm^3)	10,230	24,210	17,450	7,520	13,670	7,870	8,830	13,560
Rods (/mm^3)	-	-	520	-	-	-	90	140
Segmented (/mm^3)	8,100	23,200	13,900	6,600	11,200	5,300	5,500	7,300
Eosinophils (/mm^3)	-	-	100	-	-	300	200	100
Basophils (/mm^3)	-	-	-	-	-	-	-	100
Lymphocytes (/mm^3)	1,600	400	1,900	700	1,900	1,800	2,700	5,100
Monocytes (/mm^3)	400	400	500	100	500	300	100	600
PCR (mg/L)	-	26.7	-	20.4	-	9.4	-	36
Parameter	26/01	01/02	05/02	15/02	23/02	08/03	12/03	21/03

Source: Elaborated by the authors.

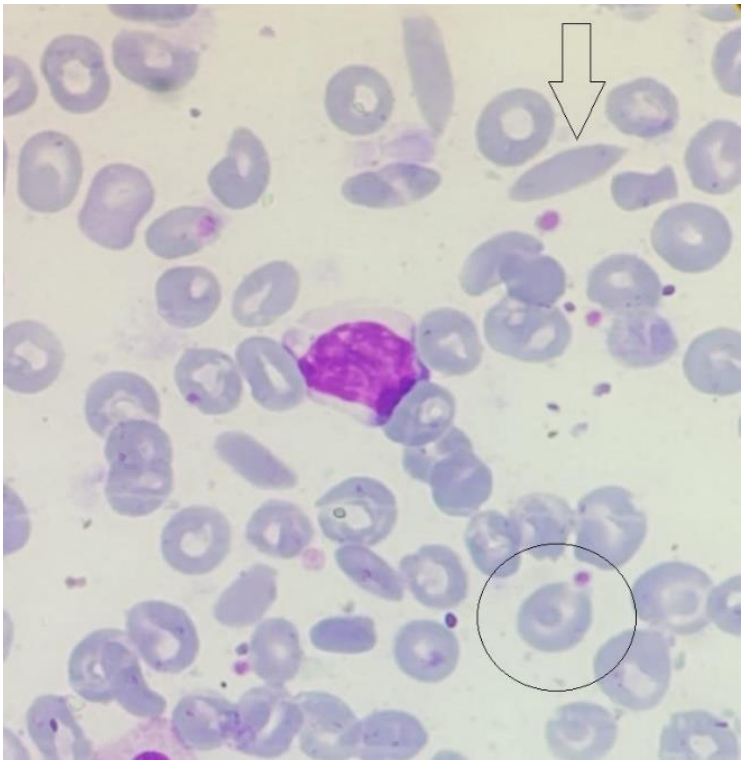
Due to the quantitative and mainly qualitative hematological alterations exhibited by the patient after antibacterial treatments, the search for abnormal hemoglobins was mandatory. It is known that prolonged therapy with antimicrobials may be responsible for the decrease in hemoglobin, which is associated with the occurrence of hemolytic anemia.[6,7]

Considering that hemolytic anemias can be autoimmune or result from membranopathies, erythroenzymopathies or hemoglobinopathies, it was

observed that the patient had a rare hemoglobinopathy of the SC type, which as a result, makes him, much more prone to the occurrence of hematological events. Blood smears showed erythrocytopenia as severe poikilocytosis with the presence of codocytes, dacryocytes, and drepanocytes.

Hemoglobinopathies are clinical conditions that have a direct correlation with the Brazilian misigenation resulting from the forced immigration of African slaves and, consequently, the racial mixing of different population groups. In this sense, codocytes (Figure 1 - circle) are target-shaped RBCs that are typically found in the circulation of patients who have hemoglobin C. In turn, drepanocytes (Figure 1 - arrow), sickle-shaped RBCs, are associated with the presence of hemoglobin S.[7,8]

Figura 1 - Codócitos e drepanócitos circulantes no esfregaço sanguíneo delgado do paciente.



Source: Elaborated by the authors.

Hemoglobin C can occur in homozygous (Hb CC) or heterozygous (Hb SC and Hb AC) states. People with hemoglobin C trait (Hb AC) are phenotypically normal and usually have no symptoms, while people with hemoglobin C disease (Hb CC) may have mild chronic hemolysis, splenomegaly, and jaundice.[1,9]

Simarlily, hemoglobin S can also occur in homozygous (Hb SS) or heterozygous state (Hb SC and Hb AS). Comparatively, HbSC hemoglobinopathy is clinically less relevant when compared to Sickle Cell Disease (Hb SS), i.e., people with HbSC have fewer acute painful episodes, fewer hemolytic crises, mild or no

anemia, and a life expectancy of about 20 years longer.[3,10]

The epidemiological relevance of hemoglobins S and C was highlighted in a cross-sectional, observational, quantitative study published in 2018 based on the internal records of the neonatal screening service of the Central Laboratory of Piauí (LACEN-PI). The research showed that 5.4% of the 69,180 samples were from newborns who were carriers of hemoglobinopathies and 4.1% of the samples were patients with sickle cell trait.[8] Furthermore, according to Rezende et al., (2018), hemoglobinopathy SC is the second most common variant of sickle cell disease in the world, just after SS anemia.[11]

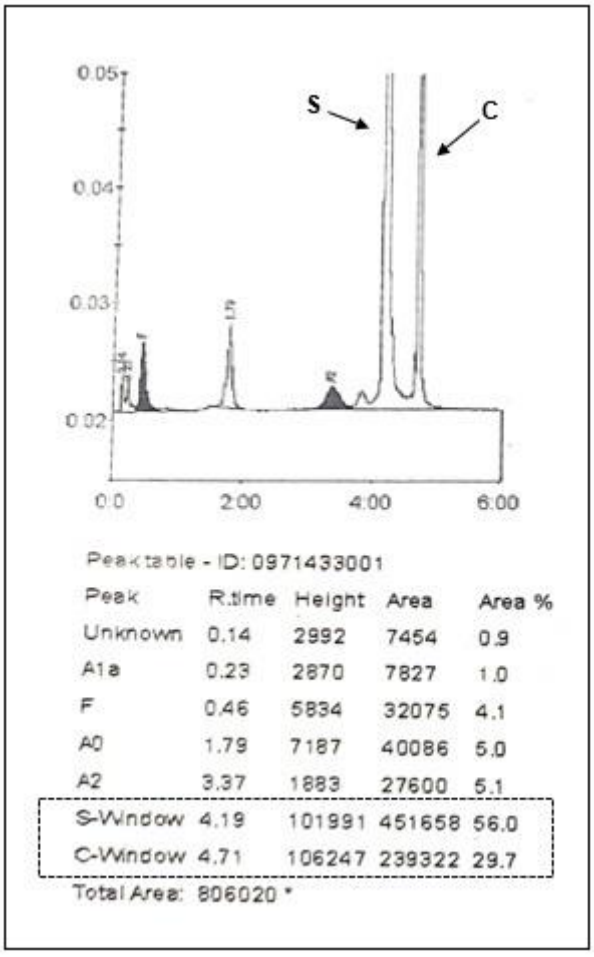
The literature asserts that non-immunological drug-induced hemolytic anemia occurs when oxidative stress-sensitive red blood cells encounter drugs that cause oxidative damage, a mechanism of direct erythrotoxicity. Furthermore, the pharmaceutical association sulfamethoxazole-trimethoprim is commonly related to non-immune hemolytic anemia, especially in patients deficient in glucose-6-phosphate dehydrogenase (G6PD).[12-16] Signs of hemolytic anemia include a decrease in hemoglobin, hematocrit, or haptoglobin levels along with an increase in indirect bilirubin and lactate dehydrogenase (LDH).[17] The patient in question was previously admitted with mild bilirubin elevation. However, due to absence of signs of hemolysis the test was not subsequently repeated.

It is worth reporting the research of Van Buren et al. (2018), who presented the case of a 9-year-old child with hemoglobinopathy SC, who reacted severely, evolving to death, due to the administration of ceftriaxone, which led to a decrease in hemoglobin from 9.3 to 2.3 mg/dL. The direct coombs test was negative for IgG and positive for C3d and C3. Similarly, the patient in this report manifested abrupt hemoglobin reduction after cephalosporin use, suggesting a correlation between anemia, antibiotic treatment, and the a posteriori diagnosed hemoglobinopathy. The observed clinical and laboratory data of the patient do not allow the possibility of a subtle hemolytic condition to be excluded.[18]

Although hemolytic anemia induced by second and third generation cephalosporins are more notorious in the literature, it is possible that such a rare deleterious occurrence may occur upon exposure to fourth generation cephalosporins, as reported by Jacobs et al., (2021) in the case of a 74 year old woman with discitis-osteomyelitis at T12 and L1 who manifested hemolytic anemia with hemoglobin of 7.5 g/dL about eleven days after starting treatment with the pharmacological association cefepime and vancomycin.[6]

Figure 2 shows the patient's hemoglobin profile. The HPLC confirmed that this was a patient with hemoglobinopathy SC with a predominance of HbS (56%) and HbC (29.9%). Given the heterozygosity, there were no apparent clinical signs of anemia and hemolysis, which makes it difficult to diagnose these situations. Therefore, understanding that the use of medications such as antibacterial, may trigger anemia and the proper interpretation of erythrogram are fundamental for diagnostic elucidation, followed by the performance of confirmatory tests, i.e., HPLC or hemoglobin electrophoresis.

Figure 2 - Hemoglobin chromatogram of the patient.



Source: Elaborated by the authors.

CONCLUSÃO

Hemoglobinopathy SC is a genetic condition, a mild variant of sickle cell disease that is often underdiagnosed. Likewise, the use of medications may reflect uniquely in the clinical condition of patients, which requires attention to signs, symptoms, and evidence revealed in laboratory test results. The present report highlights the unexpected diagnosis of a SC patient admitted due to cervical trauma. The evolution of the clinical picture with manifestation of anemia after antibiotic therapy was a preponderant factor for the diagnosis of hemoglobinopathy, a perennial condition and that makes this finding a real gain in the patient's quality of life from now on.

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