Am. J. Trop. Med. Hyg., 113(6), 2025, pp. 1442–1445
doi:10.4269/ajtmh.25-0227

Case Report

Histopathologic and Molecular Evidence of Splenic Infarction Associated with Sickle Cell Trait: An Instructive Case in Central America

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Abstract. Sickle cell trait carriers are generally considered asymptomatic; nevertheless, there are potential complications. The spleen is vulnerable to infarction because of its role in trapping and removing sickle cells and its hypoxic environment. In this report, a case of a 31-year-old physically active man who experienced severe abdominal pain near the peak of the Acatenango Volcano in Guatemala is described. At the hospital, he was diagnosed with splenic infarction, requiring splenectomy. Pathological analysis of the spleen revealed interstitial hemorrhage and marked congestion of capillaries by sickle-shaped erythrocytes. Laboratory studies revealed no evidence of anemia or any alteration in the red blood cell formula; however, leukocytosis was observed at the time of the event, which rapidly decreased on subsequent days. In contrast, platelets increased after the spleen removal. Capillary electrophoresis revealed the sickle cell carrier state. Genetic alterations associated with thrombophilia, alpha thalassemia, and other beta globin hemoglobinopathies were absent. This case reinforces evidence that high-altitude hypoxia can trigger sickle cell formation in heterozygous carriers and lead to splenic damage.

INTRODUCTION

Sickle cell anemia is a genetic pathology caused by a variant in the β subunit of the hemoglobin gene (*HBB*).[1] Traditionally, individuals carrying the variant in both alleles (HbSS) are considered to have "sickle cell disease" and are expected to be symptomatic.[2] In contrast, heterozygous carriers (HbAS) are mainly asymptomatic but can experience symptoms under stressful conditions, such as strenuous physical activity, dehydration, and high-altitude hypoxic environments.[3]

In hypoxic environments, hemoglobin S (HbS) tends to polymerize, causing erythrocytes to become sickle-shaped.[2] These sickle cells adhere to the endothelium, obstructing it and resulting in vaso-occlusive phenomena and hemolytic anemia.[1,2]

Heterozygous carriers, better known as HbS carriers or sickle cell trait carriers, primarily have hemoglobin A (HbA), despite also possessing HbS, which reduces the frequency of sickle cell formation.[2] However, it has been observed that under conditions of very low oxygen pressure, sickle cell formation occurs, causing diverse clinical manifestations.[3,4]

In HbSS patients, chronic splenic damage makes them prone to developing autosplenectomy.[1,2] There are reports of splenic infarcts in HbAS subjects, but the literature is unclear about the causality of this association and the underlying pathophysiological mechanisms.[3,5] This is the first published report in Central America detailing a splenic infarction associated with sickle cell carrier status.

CASE REPORT

A 31-year-old male patient with no known morbidity and Costa Rican Afro-Caribbean ancestry, who regularly engaged in physical activity such as hiking, experienced intense abdominal pain during a hike to the Acatenango Volcano, Guatemala, a peak of 3,976 meters above sea level. Upon admission to the clinic, he reported immobilizing abdominal pain in the left upper quadrant. A complete blood count was performed (Table 1, Day 1), and lipase was quantified, yielding a result of 31 U/L. A conservative approach was adopted, consisting of analgesic administration and close clinical monitoring. Given the lack of improvement, an abdominal ultrasound was performed, which revealed splenomegaly and lesions suggestive of ischemia in the spleen; therefore, a computed tomography scan of the abdomen was performed, which confirmed a splenic infarction (Figure 1). A splenectomy was executed, and histopathological studies of the organ were conducted (Figure 2). Splenic parenchyma revealed extensive necrosis and rupture of trabeculae and capsule, secondary to hemorrhagic infarction. There was significant congestion of capillaries by sickle-shaped erythrocytes. Sickle cells were also identified in the interstitial hemorrhage (Figure 2). Two months after the event, the patient successfully recovered and is not receiving any medication.

Considering the histopathological findings, the hemoglobin composition was analyzed via capillary zone electrophoresis using the Minicap Flex-Piercing (Sebia, Norcross, GA). An AS electrophoretic pattern was found, with hemoglobin percentages of 60.2% HbA, 36.9% HbS, and 2.9% HbA2. The HbS zone variant was confirmed by the solubility test.[6]

For molecular confirmation, *HBB* was sequenced by amplifying exons I, II, and III, as well as the promoter region, splice site, and introns I and II, using the BigDye™ Terminator v3.1 Cycle Sequencing Kit and the ABI 3500 Genetic Analyzer (Applied Biosystems, Waltham, MA). The sequences obtained were aligned with the *HBB* reference sequence (HBB Ref Seq entry at NCBI [NG_000007.3]) using FinchTV 1.4.0 software (Geospiza, Inc., Seattle, WA; http://www.geospiza.com).[7] A single heterozygous mutation was detected at codon 6 of the

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TABLE 1
Hematological parameter changes after the ischemic event

Parameter	Day 1	Day 2	Day 3	Day 4	Day 58
Hemoglobin (g/dL)	14.0	13.0	13.0	14.1	14.9
Hematocrit (%)	43.2	37.9	38.5	42.1	45.7
MCV (fL)	91.8	90.9	90.2	84.1	83.3
MCH (pg)	29.7	31.3	30.4	28.2	27.2
Platelets ($\times 10^3/\mu$L)	266	291	262	747	614
Leukocytes ($/\mu$L)	17,860	12,160	11,240	9,890	7,570

MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume.

first exon (the substitution of an adenine by a thymine), thus confirming the sickle cell trait.

To identify possible deletions compatible with alpha thalassemia, a GAP polymerase chain reaction test was performed (−20.5, Thai, −South East Asia deletion, −4.2, −3.7, Mediterranean deletion, Filipino deletion).[8] However, such deletions were not found. In addition, the genetic profile of the main alterations associated with thrombophilia was determined using the CVD StripAssay® T kit (Vienna Laboratory, Vienna, Austria). The patient under study presented a wild-type gene for Factor V Leiden (GG1691) and the prothrombin gene (GG202010).

DISCUSSION

Despite the commonly asymptomatic presentation of sickle cell trait, this case reveals that HbAS individuals may experience cell sickling under certain conditions and manifest clinical complications.

In Costa Rica, neonatal screening established in 2005 has revealed the presence of HbS throughout the country, with 1% of newborns being sickle cell trait carriers.[9] The majority of cases are reported in three provinces: San José, the capital city, accounted for 28.3% of this incidence; Guanacaste, on the Pacific Coast, was the source of 18.1% of HbAS-identified cases; and Limón, on the Caribbean, accounted for 17.2% of all cases.[9] All these areas share an important Afro-descendant presence and history in common. In fact, past studies focused on Costa Rica's afrodescendant people revealed a HbAS prevalence of 8.2% in the Pacific and 8.8% in the Caribbean community.[10]

In HbAS individuals worldwide, hematuria and proteinuria (associated with renal necrosis or carcinoma) have been reported, and vaso-occlusive phenomena can be induced by hypoxic conditions.[3,4] These vaso-occlusive events can lead to splenic infarction, priapism, hyphema, venous thromboembolisms, myocardial infarctions, and even sudden death during strenuous physical activity.[3] These manifestations are more frequent in Afro-descendants, athletes, and military personnel exposed to extreme efforts, as well as those who visit high-altitude regions.[4]

High-altitude exposure produces low oxygen tension, triggering HbS to polymerize in HbAS individuals.[11] Polymerization leads to deformed, rigid red blood cells that may obstruct small blood vessels.[11] In these conditions, the spleen is the organ most consistently injured by micro-vascular obstruction.[12] The acidic and natural hypoxic environment in the spleen, along with its anatomy, which promotes slow blood movement, may exacerbate sickling at altitude.[13] Furthermore, recent research has been conducted to study the health records of thousands of sickle cell trait carriers and evaluate the strength of the association between altitude and splenic infarction in HbAS carriers, confirming that those exposed to hyperbaric hypoxia due to altitude are at greater risk for morbidity than their sea-level counterparts.[12]

The patient hiked to the Acatenango Volcano, combining hypoxia with physical effort. Approximately 49% of splenic infarction cases in HbAS carriers have been reported to occur at more than 3,000 meters above sea level, and 29% have been reported to occur during strenuous activities.[5] Interestingly, some cases are also recorded at lower altitudes, which is why it has been suggested that other circumstances can trigger symptoms in HbAS patients.[5]

In the patient, imaging of the spleen revealed a hypodense wedge-shaped area and splenomegaly (Figure 1). Histopathological examination revealed coagulative necrosis and the presence of sickle cells. These findings confirmed that spleen ischemia was caused by microvascular occlusion due to sickle cells.[14,15]

Infections, pancreatitis, trauma, heart defects, solid tumors, and hematological malignancies are other possible causes associated with a diagnosis of splenic infarction.[15–17] Normal lipase values ruled out pancreatitis. The rapid decrease in the

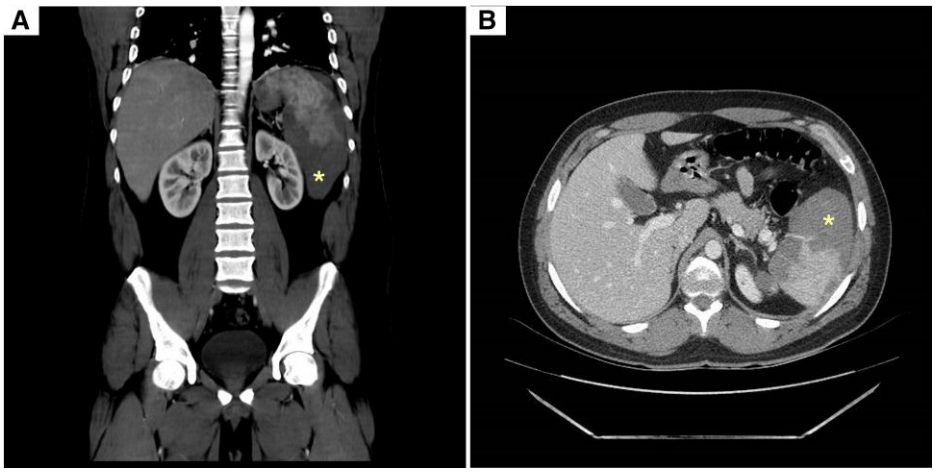

FIGURE 1. Contrast-enhanced computed tomography images revealing wedge-shaped, hypodense areas in the spleen (*). (**A**) Coronal scan. (**B**) Transversal scan.

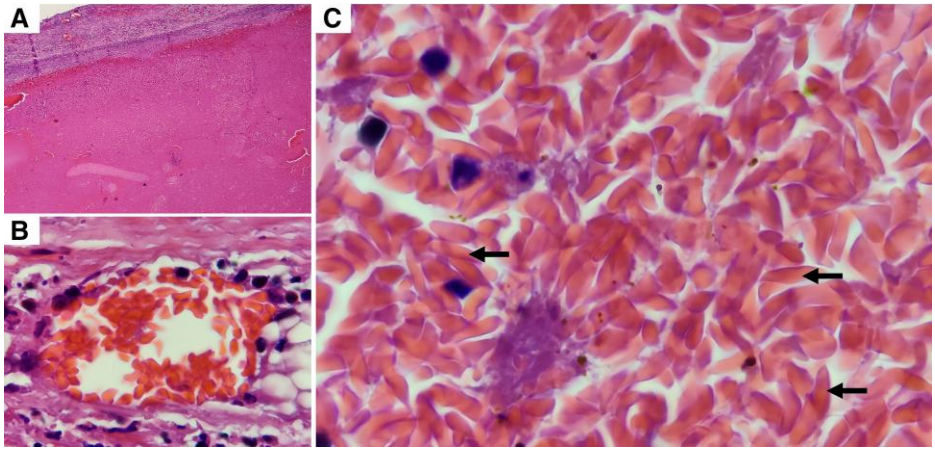

FIGURE 2. Histopathologic evidence of spleen infarction caused by sickle cells. (**A**) Necrotic spleen's parenchyma (10×). (**B**) Capillary congestion by sickle cells (100×). (**C**) Hematoxylin and eosin staining of interstitial hemorrhage revealing an abundance of sickle cells (100×). Arrows indicate three typical sickle cells.

number of leukocytes, along with clinical history, led to the exclusion of possible infections or myeloproliferative syndromes, the most relevant hematological disorder in this scenario.[15–17] In addition, imaging results ruled out the presence of malignancies in the spleen. It should be noted that thrombocytosis (Table 1, Days 4 and 58) is expected after splenectomy because the spleen normally retains one-third of the total platelets in the body; thus, its removal causes temporary thrombocytosis.[16]

Sickle cell syndrome is also present in individuals who carry double heterozygous genotypes of medical importance.[1] These are cases in which the allele that provokes HbS is accompanied by another genetic variant capable of generating a hemoglobin variant or reducing β-globin production.[3]

In this case, a double heterozygous state was ruled out by the detection of an AS electrophoretic pattern, with HbA quantities within the expected range for a carrier, a positive solubility test, and the genetic variant detected only in one of the alleles.[2] The complete blood counts (Table 1) did not reveal anemia or any alteration in the red blood cell formula, consistent with the expected heterozygous state of the patient. Finally, the possibility of an AS pattern with the coexistence of α-thalassemia was evaluated.[1,2,4] However, the main deletions that cause α-thalassemia were not detected.

Hypercoagulable states should also be considered.[18] The subject did not present with alterations in the related genetic variants (Factor V Leiden and prothrombin).[19] The patient was advised to evaluate proteins S, C, and antithrombin III and undergo other tests to rule out antiphospholipid syndrome once he had fully recovered from the event. However, the appearance of symptoms at altitude, the location in the spleen, and the observation of sickle cells at histological cuts are strong indicators for sickle cell trait as a single cause.[5]

Further studies in cohorts of heterozygous patients are suggested to support the findings discussed in the present study. The investigation of haplotypes associated with HbS[20] could be useful for identifying individuals at greater risk among sickle cell trait carriers.[5]

In conclusion, this case highlights the importance of counseling patients with HbS not only about the risk of passing the variant in the homozygous state to their offspring but also about the possible complications they could experience as sickle cell trait carriers. Additionally, it is important to reinforce training for health personnel to consider sickle cell trait as a differential diagnosis in Central America.

Received April 9, 2025. Accepted for publication July 22, 2025.

Published online October 7, 2025.

Acknowledgment: We would like to thank the patient for his willingness to participate in this case report and contribute to the better comprehension of this condition; Dr. Angel Vásquez for his support and advice; and our laboratory assistants, Lisa Buzano, Leonardo Calvo, and Daniel Guzman, for their work.

Financial support: Genetic testing and hemoglobin electrophoresis were supported by the Vice-Rectorate for Research of the University of Costa Rica as part of the research project C4338 "Update on the status of hemoglobinopathies in the Afro-descendant population of Costa Rica."

Disclosure: Informed consent was obtained from the patient as part of project C4338 "Update on the status of hemoglobinopathies in the Afro-descendant population of Costa Rica," which has been approved by the Scientific Ethics Committee of the University of Costa Rica (Certificate CEC-57-2024).

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