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CORRESPONDENCE

When a Trait Becomes a Disease: A Rare Hematologic Overlap of Sickle Cell Trait and Hereditary Spherocytosis

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To the Editor,

Sickle cell trait (SCT) is a heterozygous form of sickle cell disease (SCD) and occurs from a genetic mutation in one of two copies of the beta-globin gene, where valine replaces glutamic acid (HbS) [1]. The prevalence of SCT is around 5% in people of African ancestry in the United States [2]. Most individuals with SCT remain asymptomatic; complications typically occur only under extreme physiological stress, such as high altitude or dehydration [3]. Organ damage is rare, although the presence of SCT has been associated with chronic kidney disease (CKD) and venous thromboembolism (VTE) [3, 4]. Recent literature [2] attributes coinheritance of other red cell disorders as a risk factor for severe organ damage in individuals with SCT [5].

Hereditary spherocytosis (HS) is a red blood cell (RBC) membranopathy due to a mutation in cytoskeletal proteins, lending RBCs a spherical shape, leading to increased RBC fragility and hemolysis [6]. While individuals with HS and SCT alone have a typically mild clinical course, the coinheritance of these two conditions can result in severe clinical sequalae [7]. Prior literature on HS and SCT coinheritance demonstrates splenic sequestration or infarct as a typical complication in association with stressors, but there are no cases that describe extra-splenic manifestations [7–9]. Herein, we present a case of a 54-year-old female with SCT, HS, and a heterozygous G6PD A-pathogenic variant who presented with avascular necrosis (AVN) and proliferative retinopathy.

A 54-year-old woman of African ancestry with known SCT presented to our hematology office at the University of Cincinnati Medical Center after X-rays for right knee pain workup indicated medial femoral condyle subchondral lucency with increasing peripheral sclerosis, suggesting AVN. She had thigh and knee pain, fatigue, body aches, and left-sided abdominal pain following air travel and exercise. Labs revealed normal hemoglobin with evidence of chronic hemolysis (see Table 1). A CT scan completed 1 year prior showed normal spleen size. MRI of the right knee confirmed AVN in the lateral and medial femoral condyles.

The usual causes of AVN were investigated. She denied prolonged steroid exposure, a history of thrombosis, or connective tissue disorders. Serum protein electrophoresis and hypercoagulability workup were negative (see Table 1). She had mildly positive anticardiolipin antibodies which did not meet the Sapporo criteria of antiphospholipid syndrome (APS) [10].

Hemoglobin electrophoresis and subsequent beta-globin gene testing confirmed SCT [*HBB* c.20A>T, p.(Glu7Val)]. The incongruence between clinical symptoms and the SCT status led to testing for coinheritance of other RBC disorders. Briefly, hemoglobin-O_2 affinity (p50) and viscosity testing were normal. G6PD level was found to be slightly lower than normal at 76%, compatible with heterozygous G6PD deficiency in a female (see Table 1).

Omar Ammari and Mina Shah are co-first authors.

TABLE 1 | Laboratory and hematological workup completed for the individual with SC and HS.

Hemolysis laboratory results			
Test	**Pretreatment**	**Post-treatment**	**Reference ranges**
Hemoglobin (g/dL)	13.1	12.3	11.7–15.5
Hematocrit (%)	37.1	34.3	35.0%–45.0%
MCHC (g/dL)	35.3		32.9–36.0
Haptoglobin (mg/dL)	< 30	—	44–215
LDH (U/L)	245	—	110–270
Total bilirubin (mg/dL)	1.5	1.3	0.0–1.5
Indirect bilirubin (mg/dL)	1.19	1.2	0.0–1.1
Reticulocyte count (%)	5.24	3.61 (June 2025)	0.5–2.0
Reticulocyte absolute (/UL)	220 604	149 815 (June 2025)	20 000–80 000
Immature reticulocyte fraction	0.49	0.44 (June 2025)	0.90–0.56

Hypercoagulability tests			
Test	**Result**	**Follow up**	**Reference ranges**
Lupus anticoagulant	Possible low titer	No titer	No titer
Anticardiolipin IgA U/mL	< 9	< 9	0–11 APL
Anticardiolipin IgM U/mL	14	< 9	0–12 MPL
Anticardiolipin IgG U/mL	26	13	0–14 GPL U/mL
Anti-beta2 glycoprotein 1 IgA units	< 9	—	0–25 GPI IgA
Anti-beta2 glycoprotein 1 IgM units	< 9	—	0–32 GPI IgM
Anti-beta2 glycoprotein 1 IgG units	< 9	—	0–20 GPI IgG
Protein C activity (%)	89	—	70–130
Protein S activity (%)	82	—	55%–123%
PNH	No PNH clone	—	—
JAK2 V617 mutation	Not detected.	—	—
SPEP	Normal pattern with no monoclonal spike.		—

Hemoglobin electrophoresis			
Test	**Initial**	**Posttreatment**	**Reference ranges**
Hb A (%)	51.6	72.7	96.0–99.0
Hb A2 quant (%)	2.9	2.9	0.0–3.5
Hb F (%)	0.5	—	0.0–2.0
Hb S (%)	40.5	24.4	0.0–0.0

Other hematologic labs		
Test	**Result**	**Reference ranges**
G6PD activity (U/g Hb)	7.6	8.0–11.9
Glucose phosphate isomerase B (U/g)	54.8	40.0–58.0
Hexokinase, B (U/g Hb)	2.0	0.7–1.7
PK level (U/g Hb)	11.8	5.5–12.4
P50 mm of Hg	24.25	22.54–28.15

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; LDH, lactate dehydrogenase; MCHC, mean corpuscular hemoglobin concentration; PK, pyruvate kinase; PNH, paroxysmal nocturnal hemoglobinuria; P50, partial pressure of oxygen at which hemoglobin is 50% saturated; SPEP, serum protein electrophoresis.

Osmotic gradient ektacytometry testing revealed a curve compatible with mild hereditary spherocytosis (Figure 1). Oxygen gradient ektacytometry, which measures RBC deformability over a descending and then ascending oxygen pressure gradient [11], showed that her red blood cells start sickling at an O_2 pressure atypical for individuals with isolated SCT. The Point-of-Sickling (PoS), where HbS polymerization is accelerated, defined as the pO_2 where the deformability (as shown by the elongation index) is 95% of its maximum value, was lower than the values seen in almost all patients with sickle cell anemia, even when they have fetal hemoglobin levels higher than 35% [11]. Therefore, whole-exome sequencing was performed (see supplemental methods) and analyzed, revealing a pathogenic *SLC4A* variant (c.1030C>T, p.Arg344*) causing HS (see Figure S1), and a heterozygous mutation in her G6PD gene (A-Matera haplotype) [12], explaining her mildly low G6PD activity.

During follow-up, the patient developed worsening vision with features like SCD-related retinopathy. Diabetic and hypertensive pathologies were excluded. Given the deteriorating clinical presentation, we discussed treatment options of hydroxyurea (HU), red blood cell (RBC) exchanges, and splenectomy, given their use in SCD and HS.

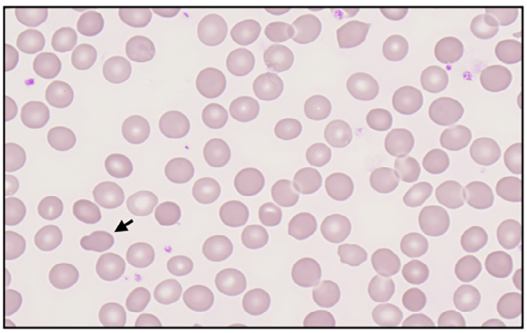
The patient favored RBC exchanges due to concerns about surgery and medication side effects. Given the lack of robust data in ameliorating retinopathy and logistic concerns, this was further modified to simple transfusions after phlebotomy. At the time of this correspondence, she has completed six treatments, reducing her HbS from 41% to 28%, with marked improvement in her fatigue and knee pain (see Table 1). A longer-term follow-up will be needed to record improvement in retinopathy.

Our patient had clinical features atypical of SCT alone, including chronic hemolysis, AVN, and proliferative retinopathy. These complications are typical of SCD and its variant forms, such as HbSC disease. Notably, chronic hemolysis is not a recognized feature of isolated SCT [1], and this prompted evaluation for coexisting intrinsic RBC disorders. Our workup led to the diagnosis of coinherited hereditary spherocytosis (HS), explaining her chronic compensated hemolysis and clinical presentation. Additionally, our patient had slightly low levels

A.

	Patient	Control	Reference Range
Omin	147	129	124-142
Elmax	0.599	0.620	0.600-0.630
Ohyp	381	417	387-443

B.



C.

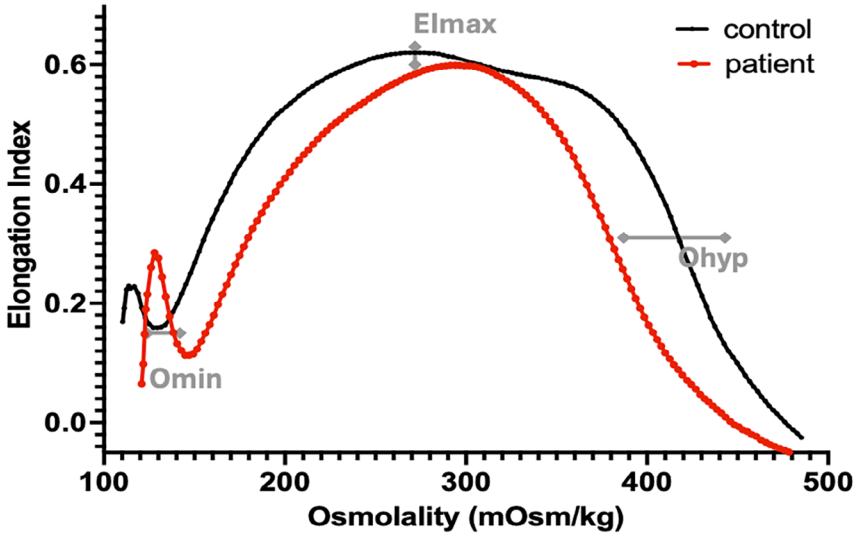


FIGURE 1 | RBC phenotype analysis: (A) osmotic gradient ektacytometry of the patient's sample processed along a normal control revealed a curve compatible with HS, with increased Omin (indicating decreased RBC surface-to-volume ratio causing increased osmotic fragility), borderline low EI max (that corresponds to the maximum deformability of the RBC) and decreased Ohyp (indicating increased intracellular red cell viscosity). (B) Peripheral blood smear reveals mild polychromasia, many spherocytes, and occasional mushroom-shaped RBCs (arrow) compatible with *SLC4A1*-associated HS. (C) Oxygen gradient ektacytometry of the patient's RBCs against a normal control sample and a representative curve from an individual with SCT. The RBC suspension is subjected to one cycle of deoxygenation followed by reoxygenation. EI (Elongation index) is plotted against the partial pressure of oxygen (pO_2). EI_{max} is the maximum EI measured at full oxygenation (pO_2 100–150 mmHg). EI_{min} is the minimum EI measured at the lowest oxygen saturation ($pO_2 < 20$ mmHg) and represents RBC deformability in post-capillary venules.

of G6PD. As G6PD levels above 60% rarely result in hemolysis, it is unlikely that this was a major determinant in her clinical phenotype [12].

Approximately 18 cases have described people with both HS and SCT [7, 8], usually presenting with splenic sequestration. Our patient's history of left upper quadrant pain after air travel aligns with these reports. However, she also had AVN and proliferative retinopathy. Our case suggests that extra splenic complications can occur in individuals with SCT and HS. These complications, hitherto, may not have been reported due to a lack of screening or attribution to other causes when identified. Mechanistically, coinheritance of SCT and HS creates a unique red cell pathophysiology similar to what is observed in HbSC disease. In the presence of SCT, increased intracellular viscosity due to HS potentiates HbS polymerization and sickling [13, 14], increasing the risk for ischemia and microvascular occlusions, possibly leading to AVN and retinopathy. In the spleen, due to its relatively hypoxic and acidic environment [15], this results in infarcts and even auto-splenectomy.

Data are scarce regarding the management of HS and SCT coinheritance, especially with extra-splenic complications. Splenectomy has been performed for patients with HS and SCT coinheritance to address splenomegaly and infarct-related pain [7–9]. This approach addresses splenic complications, but its effects on complications like AVN or retinopathy are not elucidated. Given the lack of evidence-based treatments in those with SCT and HS coinheritance, we proposed three treatment options: splenectomy, hydroxyurea (HU), and RBC exchange transfusions.

In HS, splenectomy decreases anemia, red cell intracellular viscosity, and extravascular hemolysis [11]. Therefore, we reasoned a splenectomy could decrease HbS polymerization in her RBCs. However, splenectomy is also associated with increased whole blood viscosity due to the persistence of spherocytes, which may impair microvascular perfusion, increasing the risk of thrombosis [16].

Hydroxyurea (HU) is used for disease modification in SCD [17]. We reasoned that decreasing HbS and increasing fetal hemoglobin content may protect her from further complications, though environmental stressors could still precipitate sickling. Finally, we reasoned that manual RBC exchange transfusions, also used for disease modification in SCD, would replace the patient's RBCs with healthy donor cells, reducing the effects of membranopathy and hemoglobinopathy to improve oxygen delivery, reduce sickling, and hemolysis [18, 19]. At the time of writing, the patient had completed six sessions of simple RBC exchanges and endorses improvement in symptoms of fatigue and knee pain.

In conclusion, we describe a case of an individual with concomitant HS and SCT, their clinical presentation, and management options. This case highlights the need for an alternative diagnosis and expanded workup when the clinical presentation does not match a patient's reported genotype. Through a series of laboratory investigations, we ultimately diagnosed her with HbSC-like disease and offered her treatment, underscoring the importance of taking a thorough clinical history by listening to the patient's concerns and pursuing additional laboratory studies when the clinical picture does not align with the patient's presenting symptoms.

Author Contributions

M.S., O.A., and J.G. were involved in conception and design, collected the data, drafted the manuscript, and finally approved the version to be published. M.S. and O.A. have contributed equally to the manuscript. Y.E. performed the RBC phenotypic testing, and A.H. provided genomic analysis; T.A.K. analyzed the RBC phenotype genetic testing. All authors made critical revisions and approved the final manuscript.

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The authors have nothing to report.

Ethics Statement

This case report was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Consent

The patient has consented and is aware of this manuscript. In addition, the patient has also signed a consent for the genetic testing involved. Informed consent was obtained from the patient for the publication of this report, including relevant clinical details and any accompanying images. All efforts have been made to maintain patient anonymity, and no identifiable information has been disclosed.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. G. J. Kato, F. B. Piel, C. D. Reid, et al., "Sickle Cell Disease," *Nature Reviews. Disease Primers* 4 (2018): 18010.

2. Collaborators GBDSCD, "Global, Regional, and National Prevalence and Mortality Burden of Sickle Cell Disease, 2000-2021: A Systematic Analysis From the Global Burden of Disease Study 2021," *Lancet Haematology* 10, no. 8 (2023): e585–e599.

3. R. P. Naik and C. Haywood, Jr., "Sickle cell trait diagnosis: clinical and social implications," *Hematology. American Society of Hematology. Education Program* 2015, no. 1 (2015): 160–167.

4. J. Hulsizer, W. K. Resurreccion, Z. Shi, et al., "Sickle Cell Trait and Risk for Common Diseases: Evidence From the UK Biobank," *American Journal of Medicine* 135, no. 8 (2022): e279–e287.

5. J. Z. Xu and S. L. Thein, "The Carrier State for Sickle Cell Disease Is Not Completely Harmless," *Haematologica* 104, no. 6 (2019): 1106–1111.

6. M. Risinger and T. A. Kalfa, "Red Cell Membrane Disorders: Structure Meets Function," *Blood* 136, no. 11 (2020): 1250–1261.

7. C. Ustun, F. Kutlar, L. Holley, M. Seigler, R. Burgess, and A. Kutlar, "Interaction of Sickle Cell Trait With Hereditary Spherocytosis: Splenic Infarcts and Sequestration," *Acta Haematologica* 109, no. 1 (2003): 46–49.

8. A. C. Tso, D. R. Roper, C. L. Wong, B. Bain, and D. M. Layton, "Splenic Infarction in a Patient With Sickle Cell Trait and Hereditary

Spherocytosis," *American Journal of Hematology* 86, no. 8 (2011): 695–696.

9. R. Y. Dulman, G. R. Buchanan, H. Ginsburg, et al., "Splenic Infarction due to Concomitant Hereditary Spherocytosis and Sickle Cell Trait," *Journal of Pediatric Surgery* 42, no. 12 (2007): 2129–2131.

10. S. Miyakis, M. D. Lockshin, T. Atsumi, et al., "International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Syndrome (APS)," *Journal of Thrombosis and Haemostasis* 4, no. 2 (2006): 295–306.

11. A. Sadaf, K. G. Seu, E. Thaman, et al., "Automated Oxygen Gradient Ektacytometry: A Novel Biomarker in Sickle Cell Anemia," *Frontiers in Physiology* 12 (2021): 636609.

12. C. Nannelli, A. Bosman, J. Cunningham, P. A. Dugue, and L. Luzzatto, "Genetic Variants Causing G6PD Deficiency: Clinical and Biochemical Data Support New WHO Classification," *British Journal of Haematology* 202, no. 5 (2023): 1024–1032.

13. T. A. Kalfa, "Diagnosis and Clinical Management of Red Cell Membrane Disorders," *Hematology. American Society of Hematology. Education Program* 2021, no. 1 (2021): 331–340.

14. P. G. Gallagher, "Red Cell Membrane Disorders," *Hematology: the American Society of Hematology Education Program* 2005, no. 1 (2005): 13–18.

15. J. H. Jandl and R. H. Aster, "Increased Splenic Pooling and the Pathogenesis of Hypersplenism," *American Journal of the Medical Sciences* 253, no. 4 (1967): 383–398.

16. S. E. Crary and G. R. Buchanan, "Vascular Complications After Splenectomy for Hematologic Disorders," *Blood* 114, no. 14 (2009): 2861–2868.

17. S. Charache, M. L. Terrin, R. D. Moore, et al., "Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia," *New England Journal of Medicine* 332, no. 20 (1995): 1317–1322.

18. J. Mejias, A. R. Gonzalez-Barreto, M. Rodeghier, and M. R. DeBaun, "Evaluation of Hemoglobin S Percent Threshold to Prevent Severe Pain Events: A Secondary Analysis of the SIT Trial," *Blood Advances* 8, no. 22 (2024): 5853–5854.

19. P. S. Swerdlow, "Red Cell Exchange in Sickle Cell Disease," *Hematology: the American Society of Hematology Education Program* 2006, no. 1 (2006): 48–53.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Supporting Information. **Data S1:** Supporting Information.