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Contribution: L.N. performed platelet studies and analyzed data.; K.S.-L., S.E., J.H., and B.Z. designed research, analyzed data and wrote the paper; and C.S., T.V., and M.B. took care of the patient.

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To the editor:

HbC disorders

The striking blood film entitled, “Homozygous hemoglobin C disease,” and the accompanying case report in *Blood Work* (Blood 2013;122:1694), is unlikely to represent homozygosity for hemoglobin C (HbC).¹ To establish this diagnosis, either informative family studies or DNA analysis of the β -globin genes are needed. Hemoglobin electrophoresis cannot differentiate homozygosity for HbC from compound heterozygosity for HbC and β^0 thalassemia. The typical HbC crystals in the blood film in this report are present in both conditions, and also in hemoglobin SC disease, but they cannot distinguish among these entities. More importantly for this case, electrophoresis cannot separate HbC from other hemoglobin variants that migrate on electrophoresis, like HbC, but also contain the sickle hemoglobin (HbS) mutation.² Finally, sickle vasoocclusive symptoms do not occur with HbC disease. For true sickle vasoocclusive disease, the HbS mutation must be present. HbC can crystallize in the cell, but in contrast to the example of HbS, in which polymer appears with deoxygenation, HbC crystals disappear on deoxygenation and these cells circulate normally.³

If this individual had sickle vasoocclusive events and an auto-splenectomy, she most likely was a compound heterozygote for HbC and HbC-Harlem.⁴ This variant, found in people of African descent, contains both the HbS mutation and another mutation in the same β -globin gene (β^{87} asp-asn). Rare hemoglobin variants with 2 mutations in the same gene are likely a result of crossing over between an HbS gene and a gene for another variant hemoglobin (Hb Korle-Bu in the case of HbC-Harlem). On alkaline electrophoresis, HbC-Harlem migrates like HbC, but unlike HbC, and like HbS, HbC-Harlem can polymerize when deoxygenated because it has the sickle cell β^6 glu-val mutation. Other rare hemoglobin variants with both the HbS and another mutation in the same β -globin gene also are inseparable from HbC by electrophoresis and cannot be excluded in this case.² When present as a simple heterozygote, HbC-Harlem is benign, as is sickle cell trait. When found as a compound heterozygote with HbS, it is associated with severe sickle cell disease.⁵

In this case, in which it is likely to be present as a compound heterozygote with HbC, the patient has clinical and hematologic features resembling hemoglobin SC disease.

Hemoglobin reference laboratories can sort out unusual instances in which the laboratory and clinical features of the disease are inconsistent. This can be especially important when genetic counseling is at issue.

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