Sickle Cell-Spherocytosis Associated with Hemolytic Anemia

By Mercedes V. de Torregrosa, Antonio Ortiz and Dharma Vargas

In 1949, Pauling and his associates demonstrated the existence of an abnormal hemoglobin in the blood of persons suffering from sickle cell anemia and correlated its presence with the clinical picture. They showed that sickle cell hemoglobin had different electrophoretic mobility than normal hemoglobin. Subsequently, other abnormal hemoglobins (C, D, E, G, and H) have been detected and differentiated by certain physicalchemical properties. Various hemoglobinopathies were found to be related to the inheritance of one or more of these abnormal hemoglobins.

The patient to be reported had anemia associated with the rare combination of sickle cell and spherocytosis. The clinical and hematologic data pertaining to the case are presented, and the role played by each of the two intraerythrocytic defects in the production of the hemolytic process is discussed.

CASE REPORT

C. L. V., a 5 year old white girl was admitted to the Pediatric service of the San Juan City Hospital for the first time, on January 14, 1948 because of a yellow tinge to the sclerae of 5 days duration. The mother said that the child had been apparently well except for an upper respiratory infection two weeks prior to admission. This had been followed by another upper respiratory infection 9 days later, this time accompanied by a yellow tinge to the sclera and skin. The jaundice progressed gradually, the urine became deep yellow and "stained" the clothing, but the stools remained normal in color. On the night prior to admission, the child developed a high fever and vomited on various occasions. She was brought to the hospital the following day because the jaundice was progressively getting deeper.

The past medical history disclosed four to five similar episodes of jaundice, which were all preceded by an upper respiratory infection, fever, headache, and vomiting. These episodes usually lasted for about a month and subsided gradually irrespective of the treatment given. The first such episode had occurred at the age of 2 years and the last one six months before the present admission. The child had repeated joint pains particularly in the knees, and occasionally some abdominal pains. There was no history of leg ulcers.

The family history was nonrevealing; the father and mother were living and apparently well and had negative serology. The former was a mulatto, while the mother was "white," although there was no definite proof that she was of pure caucasian origin. The paternal grandmother stated that, as long as she could remember, she had had a yellow tinge to the skin and eyes and once had an episode of deeper jaundice which lasted about two months.

The physical examination of the child showed a deeply jaundiced, pale, 5 year old girl with a few scattered ecchymoses of the legs and abdominal wall. The sclerae were icteric. There was evidence of an upper respiratory infection and mild cervical adenopathy. The heart was normal except for a short, grade II systolic murmur heard throughout the precordium, and interpreted as functional. The liver was just below the right costal margin. The spleen was slightly enlarged, rounded and not tender.

Hematologic findings were as follows: hemoglobin 7.6 Gm., red blood cells 2,720,000 per cu. mm.; leukocytes 14,200 per cu. mm.; segmented neutrophils 72%; lymphocytes

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TABLE 1—Laboratory Findings in Available Members of the Family

<table>
<thead>
<tr>
<th></th>
<th>Anemia</th>
<th>Sickness</th>
<th>Spherocytes</th>
<th>Increased fragility (saline)</th>
<th>Target cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes—0.60%</td>
<td>Yes</td>
</tr>
<tr>
<td>Father</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes—0.50%</td>
<td>No</td>
</tr>
<tr>
<td>Paternal Grandmother</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes—0.60%</td>
<td>No</td>
</tr>
<tr>
<td>Mother</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No—0.36%</td>
<td>Yes</td>
</tr>
<tr>
<td>Brother</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes—0.60%</td>
<td>No</td>
</tr>
</tbody>
</table>

28% reticulocytes; 30%; platelets 240,000 per cu. mm.; few target cells and many spherocytes were present. Wet preparations for sickling showed about 90% sickle cells after 18 hours incubation (nonfilamentous type of sickling). Serum bilirubin 3.1 mg./100 cc. Urine bilirubin was negative.

Table 1 includes the laboratory findings in the available members of the family.

Thus, the patient showed all the clinical and laboratory features of a chronic hemolytic anemia on a hereditary basis. In the presence of both sickleemia and familial spherocytosis with increased hypotonic fragility of the red blood cells, it was decided empirically that the most important factor was probably the hereditary spherocytosis. With this in mind splenectomy was advised. Even if the anemia and jaundice had been due to the sickleemia, the procedure was not expected to make the condition worse.

Splenectomy was performed on January 27, 1948. The postoperative course and convalescence were uneventful. The hemoglobin returned to near normal level and no further crises occurred. The patient’s further development was normal and the only unusual finding at present is the presence of two constitutional inheritable defects of the erythrocytes.

Pathologic Report on Spleen

Gross: The spleen weighs 210 Gm, and measures 11 x 7 x 4.8 cm. Except for a few pinhead-sized patches of thickening, the capsule is smooth and transparent. Externally the spleen is dark purple and firm. On section the pulp is dark red or brown. The trabeculae are thin and delicate. The Malpighian corpuscles are prominent but are not increased in number.

Microscopic: There is intense generalized congestion of the splenic pulp with partial obliteration of the outlines of the sinuses. The Malpighian corpuscles are of normal size and number.

Iron stain: No hemosiderin pigment is encountered. A formalin preparation from smear of the splenic pulp was inadequate because the blood was hemolyzed.

Diagnosis: Hemolytic jaundice.

Discussion

With increasing knowledge of the various types of human hemoglobins and their genetic behavior, it has become evident that various combinations of abnormal hemoglobins are not only possible, but have actually been demonstrated. Concentration of populations and improved means of transportation have provided more and more facilities for the intermixture of races, thus favoring the emergence of new genetic combinations, some favorable, some unfavorable.

In the literature there are numerous illustrations of the effect of the various known abnormal hemoglobins alone or in combination with sickle hemoglobin. The clinical and hematologic aspects of Thalassemia and spherocytosis when inherited together with other abnormal hemoglobins have also been studied.
From the clinical and laboratory findings of our patient and her family (table 1, figs. 1 and 2) it is evident that her case represents a rare combination of genes involving the inheritance of the sickle cell trait from the maternal side, and hereditary spherocytosis with increased fragility of the red cells, from the paternal side. At the time the patient was first seen by us, she was unique as far as we could tell from the literature. Recently a similar case was mentioned by Smith and Conley.16
Our patient had inherited a double constitutional defect of the red cells, but it was our impression that the familial spherocytosis was responsible for the hemolytic anemia and that the sickle cell trait had no pathologic consequences. On this basis, splenectomy was performed. The subsequent response was typical of that seen in patients with uncomplicated spherocytic anemia who undergo splenectomy. Of course, the spherocytosis and increased fragility of the erythrocytes persisted to a lesser degree after surgery; as expected, the sickling of the red blood cells was unaffected.

The patient’s brother, who presented spherocytosis of the red cells with increased saline fragility and associated mild hemolytic anemia, but no sickle cell disease, was also successfully splenectomized with complete clinical recovery.

Those individuals who are heterozygous for sickling and who also inherit a gene for another intrinsic red cell anomaly, present features which indicate the interaction of the two abnormal genes. An increase in the percentage of in-

![Figure 3](image-url)
SICKLE CELL–SPHEROCYTOSIS AND HEMOLYTIC ANEMIA

In patients who have sickle cell–hemoglobin C disease and sickle cell–Thalassemia disease (50% in sickle cell–hemoglobin C disease and up to 85% in microcytic disease), this increase in the amount of S hemoglobin, leads to intravascular sickling with its clinical signs and symptoms; the severity of the pathologic process is therefore, enhanced by the increasing amount of S hemoglobin present. Intravascular sickling does not occur in persons who exhibit only the sickle cell trait, except under abnormal conditions of reduced oxygen tension.

The hemoglobin paper electrophoretic studies done in our patient after splenectomy revealed (fig. 3): 41% S hemoglobin, 57.2% normal (adult), and 1.8% fetal hemoglobin; the latter was determined by the method of alkali denaturation of Singer. The mother's blood contained 43% S hemoglobin. Apparently in our patient there was no increase in the amount of S hemoglobin, the value of 41% being comparable to that observed in other persons with the sickle cell trait.

The electrophoretic findings and the clinical course after splenectomy in our patient indicate that the sicklemia acted as an innocuous hereditary trait superimposed upon a moderately severe type of hereditary spherocytosis.

Conclusions

1. A case exhibiting the rare combination of sicklemia with spherocytosis has been presented and discussed.
2. The importance of spherocytosis in producing the hemolytic anemia, as well as the harmless role played by the sickle cell trait is discussed. The beneficial effect of splenectomy confirmed this interpretation.
3. Studies with paper electrophoresis revealed normal adult and fetal hemoglobin values in the father, brother and paternal grandmother. Sickle hemoglobin was present in the patient's and in the mother's blood.

Conclusions in Interlingua

1. Es presentate e discutite un caso del rari combination de drepanocytemia e spherocytosis.
2. Es discutite le importantia de spherocytosis in le production de anemia hemolytic e etiam le rolo innocue del character drepanocytic. Iste interpretation eseva confirmate per le benefic effecto de splenectomia.
3. Studios exercitate per medio de electrophorese a papiro revelava normal valores de hemoglobina adulte e fetal in patre, fratre, e paterne granmatre del patiente. Hemoglobina drepanocytic eseva presente in le sanguine del paciente e de su matre.

After the completion of this paper two other abnormal hemoglobins—I and J—have been found. (Itano, H., Archives of Internal Medicine, September 1955).

References


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