The Splenic Platelet Reservoir in Sickle Cell Anemia

By Allen D. Schwartz

The presence of hypersplenism and functional asplenia occurring concomitantly in a child with sickle cell anemia prompted a study of the splenic platelet reservoir in this hemoglobinopathy. The young child with sickle cell anemia and a large spleen, who is unable to remove Howell-Jolly bodies, concentrate 99mTc sulfur colloid in his spleen, or respond to intravenous particulate antigen, retains the splenic reservoir function to pool platelets. This reservoir function is lost in the older patient in whom the spleen has become autoinfarcted. Thus, an independence of certain splenic functions is present in young children with sickle cell anemia who have splenomegaly.

The spleen is an organ of multiple functions. These include removal of damaged erythrocytes and intraerythrocytic particles, antibody formation, clearance of intravascular particulate antigen, and storage of platelets and antihemophilic factor.

It is possible there could be an independence of the various splenic activities, with separate histologic components performing distinct functions, but studies performed in asplenic individuals have not permitted such a distinction. The documentation of a state of "functional asplenia" in young children with sickle cell anemia presented an opportunity for studying possible dissociation of the various activities of the spleen.

The author recently observed a child with sickle cell anemia, massive splenomegaly, and the radiologic and hematologic criteria of functional asplenia. The child also had evidence of hypersplenism, manifested by recurrent sequestration crises and thrombocytopenia. This apparent paradox prompted a study of the splenic platelet reservoir in sickle cell anemia. Previous studies have shown that intravenous infusions of epinephrine result in a release of platelets from the spleen. This technique for assessing the splenic platelet pool was used to study a number of children with sickle cell hemoglobinopathies, asplenic individuals, and normal control subjects.

**MATERIALS AND METHODS**

The study group consisted of a total of 22 patients composed of six control subjects, four persons who had undergone splenectomy, three persons with sickle cell trait, seven with sickle cell anemia, one with sickle β-thalassemia, and one with a small accessory spleen.
SPLENIC PLATELET RESERVOIR IN SICKLE CELL ANEMIA

Post-splenectomy

E

E

%.

I,

0

450

F

0

150

C

Pre-splenectomy

Fig. 1. Epinephrine infusion study of patient T.L.

that was documented by isotopic scanning 10 yr following splenectomy for Evans' syndrome. The four younger children with sickle cell anemia, 3-6 yr of age, had palpably enlarged spleens. The older children with sickle cell anemia—12, 13, and 15 yr of age—had no palpable spleens.

An intravenous infusion of normal saline was begun on each patient. One hour later, after any effects of the venipuncture had subsided, blood was drawn from the intravenous tubing for a baseline platelet count. Epinephrine hydrochloride, in a dose of 0.0042 mg/kg body weight diluted in 50 cc of normal saline, was then given as a constant infusion over a 30-min period. The infusion was then continued with normal saline for the remaining 30 min of the study. Blood samples were removed from the intravenous tubing at 15-min intervals during the hour of testing. This dose of epinephrine has been shown to produce a significant rise in the platelet count, while producing minimal side effects in the subjects. Platelet counts were done in duplicate on all blood samples using the method of Brecher and Cronkite. The nature of the study was explained in detail in accordance with the precepts established in the Helsinki Declaration, and informed patient or parental consent was obtained.

CASE REPORT

T.L., a 6-yr-old black male with sickle cell anemia, was first seen at the Yale-New Haven Hospital in April 1969. The child had a history of sequestration crises, characterized by episodes of severe anemia and an increase in splenic size, necessitating treatment with blood transfusions. Pertinent findings on physical examination were a protuberant abdomen and a large spleen that was palpable 10 cm below the left costal margin.

The hemoglobin was 7.5 g/100 ml, hematocrit 27%, and platelet count 68,500/cu mm. Howell-Jolly bodies were seen on the peripheral blood smear. Hemoglobin electrophoresis revealed 82.6% Hb S and 17.4% Hb F. The mother had sickle cell trait. A liver-spleen scan showed no splenic uptake of 99mTc sulfur colloid despite splenomegaly. The child had documented thrombocytopenia for 2 yr, with platelet counts ranging from 60,000/cu mm to 100,000/cu mm.

An epinephrine infusion study was performed on the patient, and serial platelet counts showed a rise from 70,000/cu mm to 130,000/cu mm, a 73% rise above the baseline (Fig. 1, presplenectomy). There was a marked decrease in splenic size during epinephrine infusion. The spleen returned to preinfusion size, and platelet count returned to pre-infusion level within 30 min after the epinephrine was discontinued.

Eight months later, the child was transferred to the Yale-New Haven Hospital after having been seen at another hospital with massive splenomegaly and a hematocrit of 8%. Because of the repeated sequestration crises, an elective splenectomy was performed following transfusion therapy. Postoperatively, the platelet count rose to 665,000/cu mm.
In August 1971, 20 mo following splenectomy, an epinephrine infusion study was repeated with no rise in platelet count (Fig. 1, postsplenectomy). The child has remained hematologically stable since splenectomy, with a hemoglobin between 8 and 9 g/100 ml. No episodes of severe anemia or need for transfusion have occurred, and platelet counts have remained between 400,000–500,000/cu mm.

RESULTS

The results of the epinephrine infusion studies are shown in Table 1. In all of the control patients, a rise in platelet number occurred during the epinephrine infusion. The platelet count declined when the epinephrine was stopped and fell toward the baseline count over the next 30 min. The maximum rise in platelets over the baseline count ranged from 19% to 40%. No sig-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Baseline Platelet Count/cu mm</th>
<th>% Rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.Z.</td>
<td>8</td>
<td>312,500</td>
<td>20</td>
</tr>
<tr>
<td>M.F.</td>
<td>12</td>
<td>237,000</td>
<td>40</td>
</tr>
<tr>
<td>D.F.</td>
<td>9</td>
<td>280,000</td>
<td>26</td>
</tr>
<tr>
<td>M.O.</td>
<td>30</td>
<td>282,000</td>
<td>19</td>
</tr>
<tr>
<td>E.O.</td>
<td>8</td>
<td>325,000</td>
<td>19</td>
</tr>
<tr>
<td>D.P.</td>
<td>9</td>
<td>300,000</td>
<td>40</td>
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<tr>
<td>Sickle trait</td>
<td></td>
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<tr>
<td>L.Z.</td>
<td>9</td>
<td>310,000</td>
<td>20</td>
</tr>
<tr>
<td>C.B.</td>
<td>16</td>
<td>240,000</td>
<td>35</td>
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<tr>
<td>C.Z.</td>
<td>35</td>
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<td>Accessory spleen</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P.S.</td>
<td>15</td>
<td>242,500</td>
<td>24</td>
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<td>Sickle cell anemia</td>
<td></td>
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<tr>
<td>(A) Large spleens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.Z.</td>
<td>3</td>
<td>561,500</td>
<td>20</td>
</tr>
<tr>
<td>E.M.</td>
<td>4</td>
<td>407,500</td>
<td>17</td>
</tr>
<tr>
<td>R.L.</td>
<td>5</td>
<td>457,500</td>
<td>15</td>
</tr>
<tr>
<td>T.L.*</td>
<td>6</td>
<td>70,000</td>
<td>73</td>
</tr>
<tr>
<td>(B) No palpable spleens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.W.</td>
<td>12</td>
<td>502,500</td>
<td>5</td>
</tr>
<tr>
<td>B.D.</td>
<td>15</td>
<td>430,000</td>
<td>0</td>
</tr>
<tr>
<td>J.W.</td>
<td>13</td>
<td>500,000</td>
<td>2</td>
</tr>
<tr>
<td>Sickle β-thalassemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.D.</td>
<td>12</td>
<td>252,000</td>
<td>19</td>
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<td>Asplenic patients</td>
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<tr>
<td>H.B. (idiopathic thrombocytopenic purpura)</td>
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<tr>
<td>J.C. (systemic lupus erythematosus, hemolytic anemia)</td>
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<tr>
<td>P.C. (hereditary spherocytosis)</td>
<td>29</td>
<td>425,000</td>
<td>0</td>
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<tr>
<td>T.L.* (sickle cell anemia)</td>
<td>6</td>
<td>492,000</td>
<td>0</td>
</tr>
</tbody>
</table>

* T.L. (case report), before and after splenectomy.
significant rise in platelet count was documented in the four asplenic patients. The three patients with sickle cell trait, one child with sickle β-thalassemia, and one child with an accessory spleen had rises in platelet counts comparable to the normal controls.

Three of the children with sickle cell anemia who had palpably enlarged spleens but no clearance of radiocolloid had increases in platelet counts similar to that demonstrated in controls. Patient T.L. (case report) had a 73% rise over his baseline platelet count. The three older children with sickle cell anemia and no palpable spleen had no significant rise in platelet count. All of the patients with sickle cell anemia, except T.L., had baseline platelet counts that were over 400,000/cu mm.

DISCUSSION

Most young children with sickle cell anemia (Hb SS) have impaired reticuloendothelial activity of their anatomically enlarged spleens, a state designated as "functional asplenia." These children have Howell-Jolly bodies in their peripheral red cells, defective antibody response to intravenously administered particulate antigen, and a predisposition to overwhelming pneumococcal septicemia, findings associated with the anatomically asplenic state. In addition, the large spleens of these patients can not be visualized by isotopic scanning techniques unless the per cent of circulating Hb S is significantly reduced by blood transfusions. Despite findings of altered splenic function, children with sickle cell anemia often develop profound anemia secondary to splenic sequestration of erythrocytes, the so-called sequestration crises, and thrombocytopenia presumably due to hyper-splenism.

Penny et al. have shown that the spleen contains a pool of platelets. Although the size of this pool is proportional to the weight of the spleen, it is disproportionately greater than the amount of blood in the spleen. Intravenous infusion of epinephrine produces a transient increase in the number of circulating platelets, a response that is abolished by splenectomy.

In our studies, six normal control subjects had a rise in platelet number of 19%–40% above the base-line platelet count, while none of four anatomically asplenic individuals demonstrated a platelet rise. Seven children with sickle cell anemia could be divided into two groups. Three young children with splenomegaly had a response similar to the control subjects, and the one child with massive splenomegaly and thrombocytopenia had a 73% rise in platelet count, suggesting that a large pool of platelets was sequestered within his spleen. Three older children with sickle cell anemia and no palpable spleens had a minimal rise in the platelet count, a response comparable to that of the anatomically asplenic subjects. This indicates that these patients have little or no splenic pooling of platelets. The spleens of older patients with sickle cell anemia are shrunken and fibrotic due to progressive vascular occlusion and infarction resulting in autosplenectomy.

All but one of the patients with sickle cell anemia had thrombocytosis irregardless of splenomegaly or ability to respond to epinephrine. A greater
than normal rise in platelet count would have been expected during epi-
nephrine infusion in those with enlarged spleens, rather than the values seen. These observations suggest that the ability of a given volume of splenic
tissue to sequester platelets may be reduced in these children.

Patients with sickle cell trait and the child with an accessory spleen had a
rise in platelets comparable to the normal controls. The older child with sickle β-thalassemia had a palpable spleen and normal platelet increase. Sickle
β-thalassemia is generally a milder disease than sickle cell anemia. Patients
with this hemoglobinopathy seldom undergo autosplenectomy, and functional asplenia is not seen when isotopic studies are performed.

The apparent paradox of hypersplenic and hyposplenic function occurring
simultaneously can be explained by an independence of splenic reservoir and reticuloendothelial functions. This was demonstrated by studies in four young
children with sickle cell anemia who showed an increase in platelets counts,
indicating the presence of splenic pooling of platelets. The spleens of the same
four children were not visualized by 99mTc sulfur colloid scan. Finally, two of
these children were shown to be unable to respond to intravenous antigenic
stimuli, a defect previously reported in asplenic individuals.

The young child with sickle cell anemia who is unable to remove Howell-
Jolly bodies (pitting function), concentrate 99mTc sulfur colloid in his spleen
(reticuloendothelial function), or respond to intravenous particulate antigen
(immunologic function) retains the splenic reservoir function and pools plate-
lets as long as the spleen is enlarged. This reservoir function is lost in the
older patient who becomes anatomically asplenic due to autoinfarction. These
observations offer the best explanation for the seeming paradox of functional
asplenia and hypersplenism occurring simultaneously in young children with
sickle cell anemia.

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