Splenectomy in Sickle Cell Anemia: Report of a Case and Review of the Literature

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SICKLE CELL ANEMIA was described first by Herrick[1] in 1910. Although the disease was considered to be hemolytic in nature and many of the early patients had splenomegaly, splenectomy in this condition was reported first by Hahn and Gillespie[2] in 1927. Since that time the literature on splenectomy in this disease has consisted mainly of additional case reports. The purpose of this paper is to report a case of sickle cell anemia that was benefited by splenectomy, at least temporarily, and to review the subject of splenectomy in this disease.

Case Report

H. C., a 5 year old colored female was first admitted to the University of Virginia Hospital on December 6, 1945 complaining of abdominal pain, vomiting and sore throat. The past history revealed that the patient had swelling of the eyes and body associated with passage of dark brown urine at the age of 2. Family history revealed that the father had had syphilis. The patient's siblings and mother were in good health with no history suggestive of active sickle cell disease. Studies revealed the presence of the sickle cell trait in the mother but other members of the family were not studied.

Physical examination revealed admission temperature of 100 F. The sclerae were greenish-yellow and there was marked pallor of the mucous membranes. The tonsils were hypertrophied. Cervical, axillary and inguinal lymph nodes were moderately enlarged. The spleen was palpable and tender 8 cm. below the left costal margin, the liver was palpable 4 cm. below the right costal margin. There were no scars or ulcers on the legs. An apical systolic murmur was present. The retinal vessels were essentially normal.

Laboratory data revealed the erythrocyte count to be 1.9 M, hemoglobin 7.7 Gm., and corrected leukocyte count 11,700. A test for sickling revealed that fifty percent of the erythrocytes sickled within two hours. The blood Wasserman test was negative. Urinalysis was normal. Roentgenograms of the skull were normal.

Course in the hospital: the patient received three transfusions with marked improvement in her condition. The spleen decreased in size and extended only 5 cm. below the left costal margin following the third transfusion. Moderate epistaxis occurred several times while the patient was in the hospital. At the time of discharge she appeared greatly improved.

Following discharge from the hospital the patient continued to experience sickle cell crises at irregular intervals and for the more severe of these episodes she was admitted to the hospital five times between March, 1946 and July, 1948. These crises were characterized by fever, jaundice, abdominal pain, vomiting, headache and marked prostration. Epistaxis occurred frequently and was severe at times. Hemolysis appeared to be more pronounced with each crisis, the anemia became more severe and the spleen increased in size until on her last admission to the hospital it extended to the left iliac crest. These changes are shown in table 1. Smears of the peripheral blood revealed large numbers of normoblasts, sickle forms and target cells. There was marked anisocytosis and poikilocytosis. Bone marrow preparations obtained from the spinous process and iliac crest revealed marked hyperplasia, partic-

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ularly of the normoblasts. The test for sickling was positive on all occasions. Serum bilirubin was elevated on all admissions. Twenty-four hour quantitative urine and fecal urobilinogen[3] values were markedly elevated. Erythrocytes showed increased resistance to hypotonic saline on several occasions. The Coomb's test was negative. No circulating hemolysins or agglutinins were demonstrated in the patient's blood by the methods described by Neber and Dameshek.[4] The platelet count ranged from 37,000 per cu. mm. to 71,000 per cu. mm. and most of the time it was in the neighborhood of 50,000 per cu. mm. Bleeding time was 4 minutes or less.

The patient was admitted to the hospital on October 12, 1948 in critical condition. At that time she was again in crisis with an erythrocyte count of 0.9 M and a hemoglobin of 3.2 Gm. She was markedly jaundiced, and had moderate epistaxis. The platelet count was 50,000 per cu. mm., bleeding time was 4 minutes. Coagulation time and prothrombin time were normal. Corrected leukocyte count was 9,800 per cu. mm. Despite repeated transfusions totaling 7000 cc. of whole blood, the erythrocyte count did not rise to 3 M cells and there was no significant improvement in the patient's condition. Since the patient's condition appeared critical and showed no improvement with these measures, splenectomy was considered. The spleen was much larger than usually seen in sickle cell anemia. The platelet count and leukocyte counts were lower than usually seen during an episode of crisis. The marked increase of fecal urobilinogen and the failure to respond to transfusions seemed to indicate that the patient was

TABLE 1.—*Preoperative Data on Patient H. C.*

Date	RBC (M)	HGB (Gm.)	Spleen (cm. below left costal margin)
12- 6-45	1.9	6.5	8
3-22-46	2.5	7.0	10
3-20-47	1.5	5.5	14
12-17-47	1.46	4.0	16
7- 4-48	1.0	2.5	16
10-12-48	0.9	3.2	18

destroying transfused normal red cells as well as her own cells. Accordingly on November 5 the spleen was removed. The operation was performed without difficulty. Fifteen hundred cc. of blood were administered during the procedure. Following splenectomy there was immediate improvement in the patient's condition in all respects. In figure 1 are shown the observations made before and after splenectomy. These include erythrocyte count, hemoglobin, reticulocyte count, serum bilirubin, fecal urobilinogen,[3] plasma iron[5] and free erythrocyte protoporphyrin.[6] The patient was discharged from the hospital on November 16, 1948 and has been followed in the Hematology Clinic at regular intervals for eighteen months. She has been entirely free of symptoms, has resumed her attendance at school, and carries on normal activities without difficulty.

The following report of the spleen was given by Dr. James R. Cash, Walter Reed Professor of Pathology at the University of Virginia.

Gross description: an enormously enlarged spleen weighing 1,850 Gm. and measuring 25 x 15 x 8 cm. The spleen is quite firm and of homogenous deep purplish red color. The capsule is slightly thickened and on the whole smooth. There are a number, perhaps 24 or 30 small very shallow depressions on the surface where the capsule is slightly thicker than elsewhere. On section the cut surface has a homogenous dark red color, but nothing can be seen, which could represent the Malpighian bodies.

Microscopic: the histologic structure of the spleen is vastly altered. Most of the splenic tissue is composed of what appears to be splenic sinuses either compressed or distended with blood. These are very widely separated by spaces of the pulp which are packed almost entirely with red blood cells. The cells seen show a marked degree of sickling. There has been

a complete disappearance of splenic cells from the splenic pulp. These are entirely replaced by red blood cells. Widely scattered over this homogenous background are small irregularly shaped groups of lymphocytes which appear to represent the remains of the Malpighian bodies. Connected with each of these groups of lymphocytes, however, passing either directly through it or to one side of it is an artery. Radiating from these areas of the Malpighian bodies are large irregularly shaped blood spaces filled with blood and often surrounded by an increased amount of connective tissue. Within this connective tissue and about the walls of the arterioles are quite a few large cells having vesicular nuclei, prominent nucleoli and a moderate amount of deeply basophilic cytoplasm. Occasional cells having the morphology of megakaryocytes are seen in such areas. No actual formation of myelocytes or erythroblasts could be made out. The small scars which radiate from the surface and other areas widely scattered throughout the spleen are the sites of typical siderotic nodules which are composed of rather fibrous vascular tissue in which are embedded coiled fibers

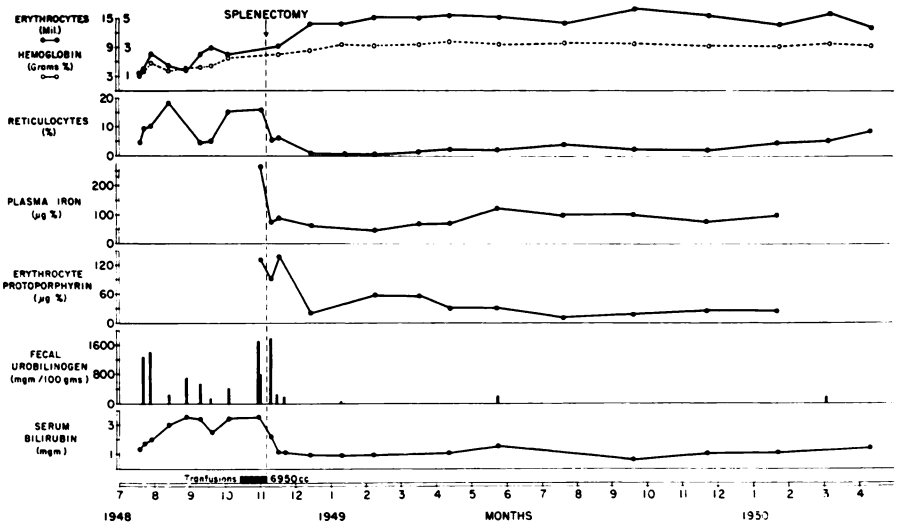

FIG. 1.—Data on sickle cell anemia patient (H. C.) before and after splenectomy.

impregnated either with calcium salts or green iron salts. Scattered in such areas are quite a number of phagocytes containing hemosiderin.

Diagnosis: unusual type of splenomegaly associated with sickle cell anemia.

REVIEW OF THE LITERATURE

In all probability some individuals with sickle cell anemia have had splenectomy and have not been reported in the medical literature. We were able to find reports of only 23 patients[2, 7-19] with splenectomy. The data from these reports are shown in table 2. The largest series, 6, was reported by Conley et al.[19] but few details of the individual cases were given. We have attempted to classify the results in the cases that have been reported in sufficient detail, as follows: *excellent*—patient became asymptomatic; erythrocyte count and hemoglobin level at normal values; in no case did this result occur. *Good*—marked amelioration of symptoms and improvement in the hemoglobin and erythrocyte count. *Fair*—slight but definite improvement in the symptomatology or in the blood.

TABLE 2.—*Results of splenectomy in Sickle Cell Anemia*

Case No.	Age Yrs.	Sex	Race	Spleen Size	Result	Follow-up Period	Author and Year Reported
1	4	M	N	Iliac Crest	Good	8 yrs.	Hahn and Gillespie,[2] 1927
2	1.6	M	N	Iliac Crest—186 Gm.	Poor	None	Bell et al.,[7] 1927
3	2.5	F	N	Umbilicus—194 Gm.	Good	8 yrs.	Cooley and Lee,[7] 1927
4	6	M	N	Not Palpable—46 Gm.	Fair	5 yrs.	Stewart,[8] 1927
5	1.5	M	N	Iliac Crest	Good	5 mos.	Hahn,[9] 1928
6	4	M	N	Iliac Crest—621 Gm.	Good	14 mos.	Landon and Lyman,[10] 1929
7	4	F	N	4 in. below LCM 200 Gm.	Poor	2 mos.	Leivy and Schnabel,[11] 1932
8	18	F	N	Not Palpable—10.5 Gm.	Poor	Died 1 d. post-op.	Ching and Diggs,[12] 1933
9	3.8	M	N	Iliac Crest—295 Gm.	Good	1 yr.	Boethe,[13] 1933
10	1	M	W	Below Umbilicus—112 Gm.	Fair	3 mos.	Cooke and Mack,[14] 1934
11	4	M	N	630 Gm.	Good	7 days	Landon and Patterson,[15] 1935
12	5	F	N	Iliac Crest—655 Gm.	Good	3.5 yrs.	Landon and Patterson,[15] 1935
13	No details			Splenomegaly	Fair	3 yrs.	Landon and Patterson,[15] 1935
14	8	F	W	Iliac Crest—480 Gm.	Good	10 yrs.	Haden and Evans,[16] 1937
15	15	F	W	Iliac Crest—700 Gm.	Good	5 yrs.	Haden and Evans,[16] 1937
16	9	F	N	Unknown	Poor	9 yrs.	Reinhard et al.,[17] 1944
17	No details				Fair	None	Cole et al.,[18] 1949
18–22	No details		N	Splenomegaly	Good	3–11 mos.	Conley et al.,[19] 1950
23	No details		N	Splenomegaly	?	6 mos.	Conley et al.,[19] 1950
24	10	F	N	Iliac Crest—1850 Gm.	Good	18 mos.	Authors' case

Poor—no significant improvement. In the reported series of splenectomy there appeared to be only one death that could be attributed to the operation.

Discussion

The relationship of the spleen to hemolytic anemia may be considered from many points of view. A valuable one is that used by Dameshek and Estren.[20] They classify hemolytic anemias as (1) those due to an "intrinsic" defect in the red cells, (2) those due to an "extrinsic" factor acting on the red cells and (3) those due to an abnormality of the spleen itself. The first group includes congenital hemolytic jaundice, Mediterranean anemia and sickle cell anemia. Splenectomy has produced excellent results in congenital hemolytic jaundice but has been considered to be of little value in Mediterranean anemia and sickle cell anemia. In the second group, those due to "extrinsic" factors, it is thought that the spleen is important as a possible source of abnormal antibodies or other factors concerned in the hemolytic process. Many cases of "acquired" hemolytic jaundice belong in this group. Splenectomy may or may not be helpful in these cases. In the third group, splenomegaly is associated with such conditions as Gaucher's disease, tuberculosis, malaria, etc., and it is suggested that the increased hemolytic activity is due to an abnormality of the spleen. In this group the anatomic enlargement of the spleen is accompanied by physiologic hyperfunction with resultant anemia, neutropenia, thrombocytopenia, either singly or in combination.

Sickle cell anemia is an inherited disorder. That the primary defect exists in the erythrocytes is shown by their abnormal shape under certain conditions, their short survival time when transfused into normal individuals,[21, 22] and the presence of an abnormal or sickle cell anemia hemoglobin as shown by Pauling et al.[23] The role of the spleen in this disease is generally considered unimportant. In our experience splenomegaly has been an inconstant finding in both adults and children, and there has been no correlation between the degree of anemia and the size of the spleen. Although the course of the disease in some patients is characterized by crises of variable severity, we have been impressed by the number of patients who seem to maintain about the same hemoglobin and erythrocyte values over a period of years. In some individuals the anemia is mild, in others moderate, in others severe, but it tends to remain relatively constant.

The patient who is the subject of this report differed from the usual pattern of sickle cell anemia. The disease increased in severity coincident with progressive enlargement of the spleen, which eventually reached a size considerably greater than we have encountered in any other patient with this disease. The patient exhibited a marked increase in hemolysis as shown by the elevated fecal urobilinogen. The fact that 7,000 cc. of whole blood in the three weeks prior to splenectomy did not raise the erythrocyte count above 3.0 M suggests that the transfused normal erythrocytes were being destroyed very rapidly. In addition, the leukocyte and platelet counts were lower than is usually the case in sickle cell anemia. The bone marrow was hyperplastic and the reticulocytes were increased.

All these observations suggested a hypersplenic effect superimposed on the usual sickle cell anemia. These considerations, the rapid deterioration of the patient's condition and the apparently hopeless prognosis led to the decision to perform splenectomy.

The rapid and marked improvement and the subsequent course have been most gratifying. The patient changed from an invalid to an active school girl. Serum bilirubin and fecal urobilinogen decreased markedly and approached the normal range. The erythrocytes and platelets returned to normal levels while the hemoglobin showed a slow increase to the level of 10 Gm. It is interesting that after the splenectomy the plasma iron level decreased to values near those seen in iron deficiency although the patient had shown evidence of excessive hemolysis and had received many transfusions over a period of some months prior to the operation. Despite an adequate diet and large amounts of iron by mouth for over one year, the hemoglobin did not rise above 10 Gm. The explanation for this divergence in rise in the hemoglobin and erythrocyte levels is not apparent. It is not certain whether this patient represents an unusual case of sickle cell anemia with a hemolytic component or whether the sickle cell process was complicated by some other unknown type of splenomegaly with a hypersplenic effect. Histologic examination of the spleen revealed several differences from that usually seen in sickle cell anemia. The possibility was, therefore, considered that the patient had developed acquired hemolytic anemia due to some other mechanism; the single negative Coomb's test does not entirely eliminate this possibility.

While the literature on splenectomy and sickle cell anemia does not warrant any definite conclusions, it suggests a possible relationship between the results of the splenectomy and the size of the spleen at the time of operation. In reviewing the reported cases in which the size of the spleen is recorded, "good" or "fair" results were obtained in 9 of 10 patients in whom the spleen extended to the iliac crest while a "good" or "fair" result occurred in only 1 of 5 patients with smaller spleens. From the published accounts of these cases, it is not possible to determine whether or not there was associated evidence of hypersplenism.

As a result of our experience in the patient recorded in this paper, and a review of other similar cases, we believe that splenectomy may be a worthwhile procedure in sickle cell anemia if the spleen is greatly enlarged, and if there are coexisting indications of hypersplenism.

Summary and Conclusions

1. A case of sickle cell anemia who had numerous hemolytic crises and also hypersplenic effects such as pancytopenia was treated by splenectomy with marked improvement in general condition and in the blood. The literature relating to this subject is reviewed. Those cases with the largest spleens appear to have shown the most striking degrees of improvement.

2. In cases of sickle cell anemia showing various indications of hypersplenism, and excessive hemolysis, splenectomy may be a rational therapeutic procedure.

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