CHRONIC LEG ULCER IN DISEASES OF THE BLOOD

By Benjamin R. Gendel, M.D.

Chronic leg ulcers have been described as a complication of several diseases of the blood and are best known in association with sickle cell anemia. Diggs and Ching reported that chronic ulcers or scars of old ulcers were present in 75 per cent of adults with this disease. However, it is less commonly appreciated that other diseases of the blood may present the complication of chronic leg ulcer. In 1925, Gänsslen mentioned a 19 year old patient with congenital (hereditary) hemolytic anemia who, over a period of nine months, had recurrent leg ulcers which resisted therapy, but healed eight days after splenectomy. Since that time over twenty patients with hemolytic anemia have been reported with chronic leg ulcers. The exact incidence of this complication is difficult to determine, but Vaughan described the occurrence of leg ulcers in three patients of a series of 18 with congenital hemolytic anemia. Taylor reported one patient with leg ulcer among 43 patients with hemolytic anemia. The combined incidence for the complication of leg ulcer in these two series is 6.5 per cent. Following the report of Taylor which summarized the previous literature, two cases were reported by Leger and Orr and another by McGovern. The ulcer complicating hemolytic anemia occurs in younger people and is located on the lower one-third of the legs. Ulcers were usually several centimeters in diameter and were surrounded by an area of pigmented skin. In half the cases, the ulcers were bilateral. In the majority of instances healing occurred rapidly after splenectomy, although the lesions proved refractory to previous therapeutic efforts.

Several French authors have noted the association of chronic leg ulcer with splenomegaly. The diagnosis in their cases is not clear, but they seem to represent patients with Banti’s syndrome of congestive splenomegaly because leukopenia and recurrent hematemesis were present. Witts reported two patients with idiopathic thrombocytopenic purpura complicated by indolent leg ulcers. His first patient was a 21 year old female with thrombocytopenic purpura of nine years’ duration. Six years earlier an ulcer appeared on the left leg which did not heal for two years. Subsequently an ulcer appeared on the right leg, but healed in less time. Both remained healed thereafter. The second patient, a 26 year old man with a lifelong history of excessive bruising and bleeding, had chronic leg ulcer for eight or ten years. The weight of the spleen removed at operation was 122 Gm. In this case there was no improvement of either the general condition or the leg ulcer after splenectomy. Witt also stated that leg ulcers occurred in Gaucher’s disease.

The unique occurrence of leg ulcer in pernicious anemia was reported by Lasch.

From the Medical Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee.

Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.
His patient had bilateral, symmetrical, deep ulcers above the ankles almost as large as the palm of one's hand. Varicose veins were not present. The patient had the typical picture of pernicious anemia with slight jaundice, histamine fast achylia, glossitis, macrocytic anemia with high color index, and megaloblastic bone marrow. The spleen was slightly enlarged. Following treatment with liver extract, healing began coincident with the reticulocyte peak on the fifth day, and the ulcer healed completely. A patient with chronic hemolytic polycythemia was described by Rau and co-workers. Their patient, a 37 year old female with a five year history of fatigue, had ulcers of the lower legs. Blood studies revealed a polycythemia, spherocytosis and increased fragility of the red cells.

It is apparent from the preceding review of the literature that leg ulceration may occur in the course of a number of diseases associated with hemolytic anemia or splenomegaly. It is the purpose of this report to describe two patients with disorders of the blood aside from sickle cell anemia, who had complicating leg ulcer, and to discuss some of the possible mechanisms for this interesting association. In one of these patients the leg ulcer was the first symptom of the disease.

**Case Reports**

*Case 1.* The patient, a 52 year old white man, entered the hospital because of recurrent right upper quadrant pain and jaundice, of seven years' duration. These attacks were intermittent and accompanied by dark urine, light stools, fever and vomiting. In May and October, 1946, the patient had similar attacks of obstructive jaundice. Splenomegaly was noted several years before admission. The patient also complained of a chronic leg ulcer just above the left ankle of about twenty-seven years' duration. This was previously considered to be a varicose ulcer despite the absence of varicose veins. A skin graft had been done in another hospital in November, 1946, prior to his admission to this hospital, and healing had progressed satisfactorily, although the healing ulcer exuded a serous fluid on dependency of the leg.

The past history revealed that since 1933 the patient had recurrent pain in both knees, occasionally accompanied by slight swelling. An uneventful appendectomy had been performed in 1931. In October, 1945, the patient was hospitalized at another hospital for an acute nephritis characterized by edema, hypertension, albuminuria, and hematuria, all of which gradually cleared up in several months.

The family history revealed no instance of a similar disease. A complete examination of all members of the family was not possible, but two siblings who were examined showed no evidence of hemolytic anemia.

Physical examination revealed an acutely ill, febrile, anemic man with moderate icterus. The blood pressure was 140/80. Heart and lungs were normal. No significant lymph node enlargement was present. The liver was not palpable but there was tenderness over the gallbladder region. Spleen was readily palpable three fingerbreadths below the left costal margin. There was a well-healed McBurney scar. An oval ulcer covered by a recent skin graft was noted just above the external malleolus of the left leg (fig. 1). It measured 2.6 cm. in its longest diameter. The remainder of the examination was not significant.

The admission blood count revealed a red cell count of 2,400,000; hemoglobin 11.5 Gm.; white cells, 9,500; 73 per cent polys; 14 per cent lymphocytes; 1 per cent monocytes; and 2 per cent eosinophils. Reticulocytes 8.4 per cent. Platelets normal. The subsequent blood counts are summarized in table 1. The serum bilirubin on admission was 1.3 mgm. Kahn was negative. Repeated urine examinations revealed a low, fixed specific gravity but were negative for albumin and sugar and no abnormal elements were found in the sediment. Repeated urea clearance tests varied between 37 per cent and 59 per cent of normal. Examination of a wet preparation of the peripheral blood revealed definite spherocytes (fig. 2). Increased fragility of the red cells in hypotonic saline was noted. Cephalin flocculation, 4 plus in 48 hours. Alkaline phosphatase, 2.6 King-Armstrong units. Prothrombin time, 88 per cent of normal. X-ray examination of the chest and both knees revealed no significant pathology.

After admission, fever continued for the first five days of hospitalization. Tests of the blood for hemo-
FIG. 1a. WET PREPARATION SHOWING SPHEROCYTES. CASE 1.

FIG. 1b. A SIMILAR PREPARATION SHOWING NORMAL BLOOD FOR COMPARISON WITH FIG. 1a.
### Table 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Red blood cells</th>
<th>Hemoglobin</th>
<th>Hematocrit vol.</th>
<th>White blood cells</th>
<th>Differential</th>
<th>Ret. count</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>millions</td>
<td>gms/100 cc</td>
<td>%</td>
<td>thousands</td>
<td>%</td>
<td>thousands</td>
<td></td>
</tr>
<tr>
<td>1-10-47</td>
<td>2.12</td>
<td>11.5</td>
<td>10.35</td>
<td>P75 L14 E1</td>
<td>8.4</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>1-17</td>
<td>3.75</td>
<td>13.2</td>
<td>9.15</td>
<td>P66 L13 M1 E1</td>
<td>5.4</td>
<td>365</td>
<td></td>
</tr>
<tr>
<td>1-24</td>
<td>3.02</td>
<td>13.6</td>
<td>8.9</td>
<td>P65 L13 E1</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-31</td>
<td>3.36</td>
<td>13.2</td>
<td>13.5</td>
<td>P78 L17 M3 E2</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy 2-3-47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>3.5</td>
<td>12.8</td>
<td>18.05</td>
<td>P96 L2 E2</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-5</td>
<td>3.75</td>
<td>12.8</td>
<td>16.4</td>
<td>P71 L16 M10 E3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-18</td>
<td>4.10</td>
<td>14.4</td>
<td>14.75</td>
<td>P63 L30 E5 B1</td>
<td>1,660</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-10</td>
<td>4.70</td>
<td>14.4</td>
<td>12.1</td>
<td>P76 L12 E1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10</td>
<td>5.3</td>
<td>15.5</td>
<td>13.8</td>
<td>P65 L13 M1 E2</td>
<td>0.8</td>
<td>836</td>
<td></td>
</tr>
<tr>
<td>5-2</td>
<td>5.6</td>
<td>16.2</td>
<td>18.8</td>
<td>P51 L13 M3 E6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy 5-6-47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-12</td>
<td>4.3</td>
<td>13.4</td>
<td>30.75</td>
<td>P84 L17 1 Myelocyte</td>
<td>430</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-6</td>
<td>4.6</td>
<td>14.0</td>
<td>11.5</td>
<td>P45 L51 E4</td>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>4.8</td>
<td>14.4</td>
<td>18.5</td>
<td>P58 L28 M14 E1</td>
<td>450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhoidectomy 7-29-47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-10</td>
<td>5.8</td>
<td>16.4</td>
<td>17.4</td>
<td>P61 L13 E5</td>
<td>0.2</td>
<td>672</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2. Case 1. Leg Ulcer after Skin Grafting.**

1286
lysins and agglutinins, using both saline and albumin as diluents, revealed no evidence of abnormal agglutinins or hemolysins. A splenectomy was performed on Feb. 3, 1947, and a large spleen weighing 1,120 Gm. was removed. Three small pieces of tissue considered to be accessory spleens were also removed. On histologic examination the latter were found to be hyperplastic lymph nodes. Following splenectomy, the patient's general condition improved remarkably and the blood count returned to normal. Spherocytes persisted, although in lesser numbers than prior to splenectomy. The ulcer healed completely and has remained well-healed ever since. On May 6, 1947, a cholecystectomy was performed. The gallbladder revealed evidences of chronic cholecystitis and contained several gallstones. A hemorrhoidectomy was performed on July 29, 1947, because of severe symptomatic hemorrhoids. The blood picture has been normal since splenectomy except for a slight persistent spherocytosis, slight leukocytosis and thrombocytosis.

Case 1. A 60 year old white man gave a history of illness since the autumn of 1943 when he was admitted to a hospital in coma with slight neck rigidity and paresis of the right external rectus muscle. There was a bloody ooz from the gums. The spleen was found to be enlarged. Spinal fluid examination revealed a xanthochromic fluid under increased pressure. Blood studies revealed a pancytopenia. A diagnosis was made of subarachnoid hemorrhage due to an underlying blood dyscrasia of unknown type. Treatment consisted of general supportive therapy including blood transfusions, as a result of which the patient gradually regained consciousness and the bleeding from the gums ceased. Further workup did not elucidate the nature of the dyscrasia and the patient returned to his home several hundred miles away. Although he was instructed to return for study on completion of his convalescence at home, he was not observed again until Dec. 1946 when he consulted a urologist because of bloody urine beginning in Nov. 1946 and persisting for four to six weeks. Studies revealed no local cause for the bleeding. A pancytopenia was again noted.

The past history revealed that seven years previously the patient had a tooth extracted and following this there was severe bleeding which necessitated blood transfusion.

The patient's father was reported to have had hemorrhage from the lung presumably due to an infection alleged not to be tuberculosis. A sister had an episode of severe bleeding following extraction of teeth.

The physical examination revealed a markedly obese, elderly, white male. Blood pressure 120/80. Heart and lungs were normal to physical examination. No lymph node enlargement was found. The abdomen was extremely difficult to palpate due to the extreme obesity but the spleen could be felt three fingers below the costal margin. The liver appeared to be enlarged two fingers below the costal margin to percussion. There was a superficial ulcer, about 4 x 6 cm., on the anterior surface of the right leg just above the malleoli. No varicosities were noted.

* The author thanks Dr. Lyle Motley of Memphis, Tennessee, for the opportunity to see this patient and for his permission to report this case.
The blood counts are summarized in Table 1. A sternal puncture revealed a nonspecific hyperplasia of the marrow.

The patient was treated with repeated transfusions and showed a slight improvement. He returned home again only to return on March 14, 1947, in a comatose condition. A history of head injury two weeks prior to admission was obtained, followed in ten days by drowsiness, progressing to coma two days before admission. Lumbar puncture revealed a bloody fluid which became clear toward the end of the tap. The patient was treated with nasal oxygen, penicillin and other supportive measures. His temperature rose progressively to 106.6°F on the third hospital day when he expired on March 16, 1947.

An autopsy was performed by Dr. A. Golden, Baptist Memorial Hospital, Memphis, Tennessee, on the same day. The salient features included the presence of the previously noted leg ulcer on the lower right leg measuring approximately 10 cm. in length and 4 cm. in width. No evidence of intracranial hemorrhage was noted. Numerous pinpoint hemorrhages were noted in the intestinal tract and the stomach and intestines were filled with a hemorrhagic fluid. Esophageal varices were noted. The liver (1120 Gm.) revealed typical hobnail cirrhosis (Laennec's) and the spleen (800 Gm.) showed congestive changes. The final anatomical diagnosis was: Cirrhosis of liver with portal obstruction; splenomegaly, portal hypertensive type; esophageal varices; and hyperplasia of the bone marrow.

**Discussion**

The first patient presented a typical hemolytic anemia, the earliest symptom of which was the leg ulcer. This proved resistant to treatment over a period of twenty-seven years and finally healed after skin-grafting and splenectomy. Based on previous reports it is possible that splenectomy alone would have been equally efficacious. It is interesting that the fundamental condition was not appreciated and the diagnosis during this time was varicose ulcer, despite the absence of varicose veins. It was impossible to determine definitely whether or not the patient had an hereditary type of hemolytic anemia, because of inability to examine all of the other members of the family, but the persistence of spherocytes after splenectomy suggested the hereditary variety. The second patient presented a difficult problem in diagnosis. At different times a variety of diagnoses were considered but the autopsy revealed cirrhosis of the liver and congestive splenomegaly (Banti's syndrome). The pancytopenia could then be explained by assuming a secondary hypersplenism which developed as a result of the congestive splenomegaly. The patient presented the unusual complication of leg ulcer in association with Banti's syndrome. Similar cases were reported previously by Lombard and Nanta, and by Gregoire and Weill.

The pathology of the ulcerated lesions of the legs has not been characteristic. Essentially, the ulcers revealed a nonspecific infiltration with inflammatory cells, sometimes associated with fibrosis and hemorrhage. The main value of biopsy would be to rule out other specific leg ulcers such as those due to syphilis or tuberculosis. Biopsies were not undertaken in either of these patients.

The pathogenesis of the leg ulcers accompanying these varied disorders of the blood has not been satisfactorily explained. In the case of sickle cell anemia, it is supposed that the general tendency to vascular thromboses might result in local thrombosis of the skin of the legs and the development of leg ulcer. However, this explanation would not satisfactorily account for the ulcers occurring in the other diseases, in which the tendency to thrombosis has not been noted. Hemolysis occurs in most of these diseases but is not characteristic of either thrombocytopenic purpura or Banti's syndrome. The common denominator would seem to be related
to the spleen. All the diseases in which leg ulcers have been noted, have been accompanied by splenomegaly, with the exception of thrombocytopenic purpura and some patients with sickle cell anemia in whom the spleen may be atrophic. In the former, evidence has been presented for a splenic inhibition of the bone marrow (hypersplenism) to account for the deficiency of platelets. Sickle cell anemia is a hemolytic anemia, and on this basis it can be assumed that there may be some excessive splenic activity accompanying the increased activity of the spleen due to sequestration of the abnormal red cells.

The rapid healing of the ulcer frequently noted following splenectomy suggests a causal relationship between the two, rather than a coincidental occurrence. It is noteworthy that prior to splenectomy many forms of treatment including bed rest have failed to produce healing. Consequently it is suggested that the leg ulcers are another manifestation of a remote effect of the spleen, perhaps a form of hypersplenism mediated in a manner not yet known.

**Summary**

The literature pertaining to the association of chronic leg ulcer with diseases of the blood other than sickle cell anemia has been reviewed.

Two patients with this association have been presented. One patient had a hemolytic anemia and the other a pancytopenia (secondary hypersplenism) in association with congestive splenomegaly due to cirrhosis of the liver.

It is suggested that the association of leg ulcer with these various diseases of the blood is related in an unknown manner to either splenomegaly or hyperfunction of the spleen (hypersplenism).

**REFERENCES**

CHRONIC LEG ULCER IN DISEASES OF THE BLOOD

BENJAMIN R. GENDEL