ULCERS OF THE LEG IN MEDITERRANEAN DISEASE

By J. Earle Estes, M.D., Eugene M. Farber, M.D., and J. M. Stickney, M.D.

MEDITERRANEAN disease, better known as Cooley’s anemia, has been recognized as a distinct clinical entity for only a little more than two decades. In spite of this fact, an extensive literature on this comparatively rare disease has been developed and has recently been reviewed by Wolman and Dickstein. It was not recognized until recent years that Mediterranean disease occurred in adult persons as well as in children. What was formerly considered to be a severe, invariably fatal disease of childhood has been found to be a disease which varies greatly in severity. It may be so mild as to give rise to no clinical symptoms. A carrier state has been thought to exist in which, although a person does not have symptoms of Mediterranean disease, he may pass on to his progeny a genetic trait which ultimately may result in a clinically recognizable form of the illness. Thus, Mediterranean disease can exist in a patient of any age, and it may be severe, mild or clinically detectable only by a thorough study of the blood.

Three adult patients who had Mediterranean disease of varying severity were studied at the Mayo Clinic in October of 1946. They were sisters of Italian descent; all 3 at one time or another had had ulcerations of the skin of the legs. A study of the literature on Mediterranean disease has failed to disclose mention of ulcers of the leg occurring in this type of anemia. It is the purpose of this paper to report ulceration of the skin of the legs as a manifestation of Mediterranean disease. Each of these patients stated that she had been anemic many years, and that a diagnosis of Cooley’s anemia had been made many times.

The first patient was a 30 year old Italian woman who complained of soreness in the right upper abdominal quadrant. She had been informed by her local physician that she had gallstones. When she had been 14 years old, ulceration of the skin over the medial aspect of the left ankle had developed. This had lasted about a year and had healed slowly, leaving a scar. During the general physical examination moderate pallor of the oral mucous membrane was seen. There was tenderness to deep palpation in the right subcostal region, and the tip of the spleen could be felt 4 cm. below the left costal margin. A small pigmented scar was seen over the medial aspect of the left ankle. There were no other significant physical observations. Except for the ulcers on the leg, this patient had not been incapacitated by her disease.

The second patient was 23 years old. She came to the clinic because of an ulcer of the skin on her right leg. When she had been 12 years of age, two ulcers over the midportion of the right leg had developed. These had lasted for two years and finally had healed, leaving scars. At 15 years of age an ulcer above the right lateral
malleolus had appeared and had lasted for two years before it healed. At 20 years
an ulcer had developed above the left lateral malleolus. This had been treated with
balsam of Peru, but at the time of the examination it had not healed. In spite of
long-existing anemia, in which the patient said the value for hemoglobin had
averaged 8 Gm. per 100 cc. of blood for many years, she had not been incapacitated
except by the ulcers of the leg. During the general physical examination a yellow
pallor of the skin was noted. A systolic murmur was heard over the entire pre-
cordium. The spleen was palpable 7 cm. below the left costal margin, and the liver

![Image](https://example.com/image.jpg)

**Fig. 1.** **Indolent Ulcer on the Left Leg of a Female Patient Twenty-three Years Old Who Had Mediterranean Anemia. Note the Atrophic Scars at the Sites of Old Healed Ulcers**

was enlarged to a point 3 cm. below the right costal margin. An ischemic-appearing
indolent ulcer 4 cm. in diameter was present on the lateral surface of the left leg
above the external malleolus (fig. 1). The border of this ulcer was irregular, but
was not undermined. There was considerable hyperpigmentation at the periphery
of the ulcer, but in this zone there was only minimal cutaneous sclerosis. The base
of the ulcer was clean. Three scars, the sites of previous ulceration, were noted (1)
on the right leg, (2) on the anterior surface of the left leg, in its upper third part
and (3) on the lateral surface of the left leg. These scars had a hyperpigmented
periphery and a glossy, atrophic center. There were no other significant physical
observations.
The third patient was 19 years old. She came to the clinic because she had an ulcer on her right ankle which had remained unhealed for a year. When she had been 17 years old an ulcer on the left ankle had developed which had been treated with penicillin without apparent effect. This ulcer had healed slowly over a period of eighteen months. A year later an ulcer on the right ankle had appeared and had been treated with balsam of Peru, but it had not healed.

During the general physical examination pallor of the mucous membranes and yellow pallor of the skin were noted. The heart was enlarged and the apical impulse could be palpated at the anterior axillary line. A loud blowing systolic murmur was heard over the entire precordium, and it was maximal at the cardiac apex. Dyspnea was evident when the patient was at rest, and was pronounced after any exertion. The spleen extended to the umbilicus, and the liver was palpable 7 cm. below the right costal margin. A triangular ulceration of the skin 1.5 cm. in diameter was noted just distal to the right external malleolus. This ulcer was similar to the one described in the second patient. The present patient was suffering from a severe form of Mediterranean disease, and was greatly handicapped.

In none of these patients was there evidence of arterial or venous insufficiency in the extremities. Local treatment for the ulcers and the administration of iron, liver extract and whole blood had not brought about any improvement in the ulcers or the general health of the patients. In roentgenograms of the skull, only those of the third patient demonstrated changes of significance. General osteoporosis, with thinning of both the inner and outer tables of the skull, was noted.

In smears of specimens of blood from all 3 patients similar changes characteristic of Mediterranean disease were seen. The changes were of a severity in proportion to the extent of the anemia. These changes consisted of a great variation in the size and shape of erythrocytes, with many microcytes but no spherocytes. Hypochromasias and polychromatophilia were marked, and normoblasts were present. Target cells were seen in all smears, but they were not conspicuous. Myeloid immaturity was not noted.

Studies of sternal bone marrow were made in each case. In all three there was hyperplastic erythropoiesis of the normoblastic type. Megaloblasts were not seen. It may be of some significance that the mature erythrocytes in the marrow smears were of more uniform size and shape than were those seen in specimens of peripheral blood. Pertinent laboratory data are summarized in table I.

The diagnosis of Mediterranean disease was made in these three cases on the basis of familial anemia, increased resistance of the erythrocytes to hemolysis in hypotonic solution of sodium chloride, very active normoblastic erythropoiesis, and the failure of the anemia to respond to any therapy. No other cause for the anemia could be found. Sickle cell anemia was eliminated by the absence of sickling, and congenital hemolytic icterus, had it been present, should have produced spherocytosis and increased fragility of the erythrocytes.

A piece of skin was removed for biopsy from the margin of the ulcer on the leg of the 23 year old patient. Epidermal changes consisted of minimal hyperkeratosis and irregular acanthosis. In the upper half of the cutis the capillaries and arterioles
were increased in size and number, and there was moderate infiltration of lymphocytes, connective-tissue cells, chromatophores and polymorphonuclear leukocytes. In the midportion of the cutis there were several areas of beginning necrosis with

<table>
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<tr>
<th>Test</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, grams per 100 cc.</td>
<td>10.0</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Erythrocytes, per cubic millimeter</td>
<td>4,140,000</td>
<td>4,140,000</td>
<td>2,870,000</td>
</tr>
<tr>
<td>Leukocytes, per cubic millimeter</td>
<td>10,900</td>
<td>11,500</td>
<td>6,300</td>
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<td>Erythrocyte fragility in sodium chloride</td>
<td>.42−.28*</td>
<td>.46−.28*</td>
<td>.44−.28*</td>
</tr>
<tr>
<td>Beck and Hertz</td>
<td>No sickling</td>
<td>No sickling</td>
<td>No sickling</td>
</tr>
<tr>
<td>Serum bilirubin, milligrams per 100 cc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect</td>
<td>1.3</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Fecal urobilinogen, milligrams (24 hour</td>
<td>109</td>
<td>188</td>
<td>223</td>
</tr>
<tr>
<td>excretion)</td>
<td>169</td>
<td>289</td>
<td>244</td>
</tr>
</tbody>
</table>

* Incomplete.

**Fig. 2. Specimen Taken for Biopsy from the Margin of an Ulcer on the Leg of a Patient with Mediterranean Anemia, Showing Dense Deposits of Iron in the Midportion and Lower Portion of the Cutis (Hematoxylin and Eosin X25)**

disintegration of cells, so that recognition of cell types in these areas was not possible. Elastic tissue was absent throughout the upper portion of the cutis, and very little elastic tissue was present in the vessels. Degenerative changes, homo-
Genization of collagen and moderate edema were seen in the arteriolar walls. In occasional vessels there was proliferative intimal thickening, although in most of the vessels there was no significant alteration of wall-to-lumen ratio. Dense deposits of iron (fig. 2) were seen in the midportions and lower portions of the cutis stained with ferric thiocyanide.

The dense deposits of iron in these sections are of great interest. Whipple and Bradford have studied the deposition of iron-containing pigment in the organs of patients who died of Mediterranean disease. They considered this pigment to be as characteristic of the disease as is any other finding. It resembles that seen in hemochromatosis in adult persons and is seen in most of the organs of the body. Whipple and Bradford made no mention of such deposits in the skin. Mills has reported results of a postmortem study of the skin of a child who died of Mediterranean disease. He considered the pigment he found to be melanin, and not hemosiderin.

When the differential diagnosis of ulcers on the legs of these patients was considered, it was apparent that the lesions were not secondary to occlusive arterial diseases such as thrombo-angiitis or arteriosclerosis obliterans. The absence of hypertension excluded the possibility of the ischemic type of ulceration occasionally associated with hypertension. Venous stasis could not have caused the ulcers because there were no varicose veins and chronic venous insufficiency was not present. Trophic disturbances such as might be caused by syringomyelia, tumor of the spinal cord or tabes dorsalis were excluded. Chronic granulomas as seen in syphilis, tuberculosis, sarcoïdosis or dermatomyosisis would have produced different histopathologic changes.

The ulcerations of the skin of the legs which occur in sickle cell anemia and congenital hemolytic icterus do not have a distinctive gross appearance which could be used to distinguish them from each other or from those in the patients we are discussing. It seems to us that the chronic ulcer on the leg of an anemic patient is not pathognomonic of a specific type of anemia. The exact character of the anemia must be determined by appropriate clinical and hematologic study.

**Summary**

Ulceration of the skin of the legs may occur in Mediterranean disease. Such ulceration cannot be distinguished grossly from that occurring in sickle cell anemia and congenital hemolytic icterus. The outstanding histologic feature (noted at biopsy of one of these ulcers) is the prominent deposition of iron in the cutis.

**REFERENCES**

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