The Successful Therapy with Streptokinase-Streptodornase of Ankle Ulcers Associated with Mediterranean Anemia

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The first report of Mediterranean anemia was made by Cooley and Lee in 1925. They described it as a fulminating, fatal hemolytic anemia of early childhood. It has since been recognized that the disease occurs in adults as well as children and that the severity of the disease varies over a wide spectrum. At one extreme is the syndrome originally described by Cooley, while at the other, one finds the characteristic blood picture without other clinical manifestations. The disease is inherited in a definite genetic pattern being limited almost, but not entirely, to persons of Italian, Greek, Armenian, or Syrian ancestry. The clinical manifestations and laboratory data, as well as the more common variations and complications of Mediterranean anemia, have been amply discussed in the extensive literature compiled in the twenty-eight years since it was first reported.

It is the purpose of this paper to present a successful mode of therapy for ulcerations of the skin of the legs occurring as a rare complication of Mediterranean anemia.

CASE REPORT

Mrs. A. V., a 29 year old Italian housewife, was admitted to the George Washington University Hospital with the chief complaint of ulcers on the medial sides of both ankles, a condition of three years duration. Her present illness began eighteen years prior to admission, at age 11, when she had an acute episode of jaundice. She was admitted to a hospital and found to have an enlarged spleen, with hematologic studies consistent with Mediterranean anemia. Investigation of her immediate family revealed no evidence of the disease in her parents or siblings. The jaundice subsided and the patient remained well until ten years prior to admission, at age 19, when she noted the spontaneous onset of a pinpoint ulceration on the medial side of her left ankle. The ulcer continued to spread despite local therapy and one month later was approximately 1 inch in diameter. For one year, in spite of bed rest and the application of various salves, there was no change. Closure was finally accomplished by a skin graft. On ambulation, however, the grafted area degenerated and the ulcer reverted to its original condition. Ten months later, a second skin graft was unsuccessful. During the following three years various forms of therapy were tried without effect. Five years prior to admission, mecholyl iontophoresis was used with healing.

Three years prior to admission, at age 26, the patient was married and shortly thereafter became pregnant. As a part of her prenatal care, she received 500 to 1000 cc. of whole blood at monthly intervals. With the advancement of her pregnancy she began to note respiratory embarrassment. This was attributed to her enlarged spleen and splenectomy was performed at the sixth month of gestation with uneventful recovery. In the latter months of pregnancy, she developed ankle edema with subsequent appearance of ulcers on the medial sides of both ankles. These were at first pinpoint in size but gradually increased to 1 inch in diam-

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eter. Following delivery, the edema subsided with some decrease in the size of the ulcers; however, complete healing was never noted. One and one-half years prior to admission, the patient again became pregnant. The ulcers followed the same pattern noted above. From the time of delivery to admission, the ulcers remained unchanged.

Physical examination at the time of this admission, revealed vital signs: temperature 37 C., pulse 80, respirations 18, and blood pressure 106 systolic and 56 diastolic. The skin over both ankles and feet was darkly pigmented. Over the medial aspect of each malleolus there were circular ulcers surrounded by a 1 to 2 cm. zone of erythema. The right ulcer measured 6.6 cm. in diameter while the left measured 4.5 cm. Both ulcers were covered with a dry yellowish crust and were nontender.

Laboratory data were as follows: hemoglobin 8.7 Gm., hematocrit 30, white blood count 4150 with 72 per cent polymorphonuclear cells. The blood smear showed 292 nucleated red cells per hundred white cells. There were many target cells, as well as polychromatophila, anisocytosis, and poikilocytosis. No sickling was noted on any preparation. Fragility studies showed hemolysis beginning at 0.42 and complete at 0.34 per cent saline for the control, and 0.42 and 0.28 per cent saline for the patient. Urine analysis was normal. Serum proteins 7.85 Gm. per cent, albumin 4.37 Gm. per cent and globulin 3.48 Gm. per cent. Thymol turbidity 10.5 units. Bilirubin 0.15 mg. per cent direct, 0.39 mg. per cent indirect. Serum studies showed hemolysis begins at 0.42 and complete at 0.34 per cent saline for the patient. Thrombosis and endothelial changes were noted on various occasions.

The patient was placed on bed rest and not allowed to place her legs in a dependent position at any time. She was given a high protein, high calorie diet with vitamin supplements. Despite adequate chemotherapy, Priscoline, and continuous aluminum acetate moist dressings, the ulcers remained unchanged. On the third hospital day, 100,000 units of streptokinase (SK) and 25,000 units of streptodornase (SD) (Varidase, Lederle) mixed in 30 Gm. of a water miscible cream was applied to the ulcer four times a day. All preparations containing SK-SD were stored at 10 C. By the fifth hospital day, the crusts had dissolved and by the seventh hospital day, the craters were filled with new granulation tissue. On the twelfth hospital day, the cream was discontinued and moist dressings saturated with 400 units of SK and 50 units of SD per ml. of normal saline were instituted. These were applied continuously with the exception of one hour each morning, when the ulcers were exposed to air. This regimen was continued until the sixteenth hospital day. At this time, due to the marked proliferation of granulation tissue in both ulcers, they were covered with powdered sugar four times a day in order to induce osmotic shrinkage of the tissues. By the eighteenth hospital day, both ulcers presented a clean, flat, granulating surface. Around the margins there was evidence of epithelialization. The powdered sugar was discontinued and the SK-SD applications in the form of moist dressings was reinstituted. These were continued for three days with a gradual increase in the height of the granulation tissue. It was now apparent that the ulcers had begun to decrease in size. The moist dressings were continued during the day and powdered sugar was applied at night. The patient was discharged to continue this therapy at home. No antibiotics were employed. During her twenty-seven days of hospitalization she had received 3500 cc. of whole blood. Her hemoglobin rose to 12.7 Gm.

On the above regimen, the ulcers progressively decreased in size and approximately six weeks after therapy was first instituted, there was complete epithelialization of both ulcers. All medications were discontinued. The newly healed areas were protected with sponge rubber held in place with elastic stockings. She was followed thereafter on an outpatient basis with transfusions at monthly intervals. Her hemoglobin varied from 7.3 to 11.1 Gm. on various occasions. Nucleated red blood cells varied from 60 to 150 per 100 white blood cells.

She resumed all normal activities and had no further difficulty for approximately six months. At that time she became pregnant. Three months later edema of both ankles was noted and small ulcerations reappeared on both ankles. As pregnancy advanced the ulcers increased progressively in size and by term appeared as they had on her previous admission. Following delivery, a bilateral tubal section and ligation was performed. On the fifth hospital day, 100,000 units of SK and 25,000 units of SD in 30 Gm. of carboxymethylcellulose jelly (CMC, Lederle) was applied to the ulcers four times a day and continued thereafter.
at home. The patient remained at bed rest. After approximately three weeks, proliferation of granulation tissue was so marked that the previous regimen with powdered sugar was again employed. This was applied at night while the SK-SD in CMC jelly was used during the day. Within eight weeks after the institution of therapy, the ulcer on the right ankle was completely re-epithelialized and the ulcer on the left ankle had decreased to 1.5 cm in diameter. Despite ambulation at this time therapy was continued. The ulcer on the left ankle continued to heal but at a considerably slower rate. Over a two month period it gradually decreased in size and finally healed. The ulcers have remained healed to the present, six months after the institution of the second course of therapy.

DISCUSSION

Leg ulcers in Mediterranean anemia are rare, having been reported only three times before. These authors found that the ulcerations healed very slowly, if at all, that the healing was by scar formation, and that recurrences were common. Only one case of the five reported was free of ulcers at the time of the reports.

The use of streptokinase-streptodornase proved to be very successful in the treatment of the ulcers in the patient reported here. These agents, if applied properly, are extremely useful in the treatment of infected superficial wounds, the causes of which may be extremely varied. They were applied, in this case, in a water miscible cream, as continuous moist dressings and in carboxymethylcellulose jelly.

Carboxymethylcellulose jelly, as a vehicle for streptokinase-streptodornase, is ideally suited for use on superficial areas. A minimal amount of SK-SD in the jelly produces an adequate and prolonged concentration at the site where they are needed. It can be used by the patient without difficulty and does not require the inactivity which would be necessary if the SK-SD was applied in the form of moist dressings or by a constant drip.

SUMMARY

1. A successful method of treatment of chronic leg ulcers associated with Mediterranean anemia, employing streptokinase-streptodornase in carboxymethylcellulose jelly, is presented.
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