IMAJ • VOL 13 • MAY 2011

Healing of Refractory Leg Ulcer in a Patient with Thalassemia Intermedia and Hypercoagulability after 14 Years of Unresponsive Therapy

Carina Levin MD and Ariel Koren MD

Pediatric Hematology Unit and Department of Pediatrics B, HaEmek Medical Center, Afula, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: thalassemia intermedia, leg ulcer, thrombophilia, factor V Leiden

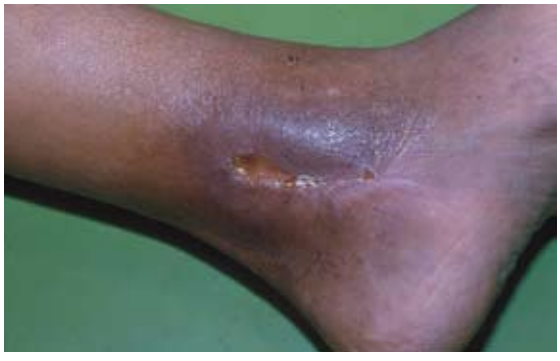
IMAJ 2011; 13: 316–318

Chronic leg ulcers, specially in patients with thalassemia, are dificult to cure [1]. Understanding the underlying phatogenesis is crucial for successful therapy. Hypercoagulability was recently shown to contribute to the etiology and perpetuation of leg ulcers [2]. We present a patient with thalassemia intermedia, post-splenectomy with a factor V Leiden mutation and chronic leg ulcer that had not healed for 14 years.

PATIENT DESCRIPTION

A 35 year old woman with beta-thalassemia intermedia, homozygous for the IVS1,1 mutation, had suffered for 14 years from a chronic non-healing ulcer on her left leg [Figure]. The patient was diagnosed at age one year with beta-thalassemia and received regular blood transfusions until the age of 6 when she underwent a splenectomy due to severe hypersplenism. She was then prescribed low-dose aspirin for thrombocytosis and received sporadic blood transfusions as required. She was found to be heterozygous for the factor V Leiden mutation (G1691A). All other genetic and plasmatic thrombophilic analyses were normal. No thrombotic events were ever diagnosed. Chelation therapy with deferoxamine was started at age 12; at age 21 regular blood transfusions were again required.

Leg ulcer in the internal malleoli



Her current medical treatment includes subcutaneous infusion of desferrioxamine, folic acid, low-dose aspirin, oral penicillin, allopurinol (due to hyperuricemia), calcium, vitamin αD3 and alendronate.

At age 19 the patient developed an ulcer in the internal malleoli area of the left leg [Figure]. For a year before emergence of the ulcer, her mean hemoglobin level was 6.7 g/dl and fetal hemoglobin 96.8%. During that year she was treated with folic acid, low-dose aspirin and allopurinol and did not receive regular blood transfusions.

For the leg ulcer, different local therapies were used including antibiotics, hyperbaric oxygen therapy, skin autologous graft transplant and local applications of macrophage suspension. In addition to the local treatment, systemic therapeutic options were employed including systemic antibiotics and antimicotic therapy as well as systemic hyperbaric oxygen therapy that was administered in a hyperbaric chamber. There was no improvement in her condition.

Between the ages of 20 and 29 the patient underwent different therapeutic approaches including oral hydroxyurea, regular blood transfusions every 3 weeks, combined therapy of oral hydroxyurea and regular blood transfusions or sporadic on-demand transfusions. Only transient and incomplete healing of the ulcer was achieved.

At age 29 a new blood transfusion regimen of one unit of packed red cells every 3 weeks was started, in addition to hydroxyurea therapy and desferrioxanine. During that year the pre-transfusion mean hemoglobin level was 7.9 g/dl and HbF 48%. No clinical improvement was seen. At age 32, the blood transfusion regimen was increased to two units of packed red cells every 3 weeks with the patient still receiving hydroxyurea and desferrioxamine. The pre-transfusion mean hemoglobin level was 9 g/dl, HbF 23% and hemoglobin A 63%. Towards the end of the second year of this protocol the leg ulcer was completely healed, and there was no recurrence for more than 2 years of follow-up with the same treatment.

COMMENT

Leg ulcers are a common complication of thalassemia intermedia, occurring in as much as one-third of patients with untreated or poorly controlled disease. They usually appear in the second decade of life and are generally located on the medial

HbF = fetal hemoglobin

or lateral malleoli. The ulcers emerge after a minor trauma and tend to expand rapidly [1]. They are slow to heal and tend to recur or become chronic, causing severe pain, disability and esthetic problems that are difficult to manage for both patients and physicians.

The etiology of thalassemic leg ulcers seems to be multifactorial with the main pathogenic mechanism appearing to be tissue hypoxia secondary to the anemia and the high affinity of fetal hemoglobin for oxygen, since fetal hemoglobin causes shifts in the hemoglobin-oxygen dissociation curve toward higher oxygen affinity, resulting in tissue hypoxia [3]. The percentage of HbF in thalassemia intermedia patients varies greatly, ranging from 5% to almost 100% depending on whether the genotype is β^+ or β^0 thalassemia.

Others factors contributing to ulcer formation include: a) abnormal rheological behavior of the diseased erythrocytes characterized by increased rigidity of their cellular membrane and enhanced adherence to endothelial cells, b) local edema due to venous stasis and possibly right heart insufficiency, c) repetitive local trauma and skin infections, and d) hypercoagulablility and prothrombotic tendency [2].

The presence of hypercoagulability in thalassemia patients is well known. Several etiologic factors may play a role in the pathogenesis. The specific changes in the lipid membrane composition of the abnormal red blood cells and the hemosiderosis may contribute to activation of the coagulation process and activation of other blood cells, including platelets, monocytes and granulocytes, alone or together, which may induce activation of the vascular endothelium, further contributing to the thrombotic process [4].

Reduced levels of natural anticoagulant proteins were also reported in thalassemia patients, while a higher incidence of thromboembolic events was reported in thalassemia intermedia patients. Venous thrombosis is more prevalent in patients who do not receive regular transfusions and who have undergone splenectomy. Those patients may be more susceptible to thromboembolism because they have more circulating damaged red blood cells and increased platelet counts [4].

Hypercoagulable disorders may contribute to the development and poor healing of leg ulcerations, either indirectly as a consequence of venous thrombosis, or directly by thrombus formation in small arteries, arterioles, capillaries or venules. A recent study reports that in a cohort of 30 patients with chronic leg ulcers 70% were associated with one or more thrombophilic factors [2]. Prothrombotic states and antiphospholipid antibodies are thought to contribute to vasculopathy and leg ulcers in patients with connective tissue diseases [5]. Successful treatment with anticoagulants was reported in some cases.

The treatment of leg ulcers in thalassemia is based on various conventional local measures such as banding, bed rest, avoidance of trauma and venous congestion, local hygienic precautions, antiseptic dressings, and local or systemic antibiotics. Other proposed measures are local administration of hyperbaric oxygen, topical synthetics, cellular matrixes, topical platelet-derived factors, skin grafting, local injections of granulocyte-macrophage colony-stimulating factor, and topical macrophage applications. Systemic treatments include oral administration of pentoxifylline in order to improve the blood flow and relieve the venous and lymphatic outflow. Treatment with high doses of ascorbic acid was also described. Healing of leg ulcers in thalassemia intermedia patients after oral administration of hydroxyurea was also reported and is likely due to improved rheological conditions of thalassemic red blood cells and their reduced adhesion to the vascular endothelium.

In thalassemia patients hydroxyurea therapy raises the total hemoglobin levels by raising HbF; the amelioration of the anemia is reflected in the clinical benefits reported [3]. The effect of hydroxyurea on the thalassemic red blood cells is not completely understood. The basic hypothesis is that the increase in the gamma globin chain synthesis alleviates the β/α globin chain imbalance and decreases the damage produced by the excess of alpha-chains that precipitate in the red blood cells. The subsequent effect is an improvement in red blood cell morphology. Previous studies show that low doses of hydroxyurea increase the HbF content in erythroid cells with a consecutive increment in total hemoglobin. The final effect of hydroxyurea in thalassemic patients can then be related to an improvement in red blood cell survival.

Exchange blood transfusions have been reported to be successful in treating leg ulcers in a patient with high hemoglobin levels and high percentage of HbF. Increasing the total hemoglobin level with blood transfusions is one of the most feasible treatments of leg ulcers in thalassemia patients.

The patient presented here experienced less fatigue and had a general feeling of well-being on hydroxyurea therapy. An additional benefit is reduction of the erythropoietic activity that inhibits the expansion of the bone marrow and extramedullary erythropoiesis. Clearly, the successful treatment of any leg ulcer depends on an accurate diagnosis of the underlying etiology. Unfortunately, healing of chronic leg ulcers is not assured despite our understanding of the etiology and often requires time and persistence to find the appropriate therapy for each patient. The case reported here of a thalassemia intermedia patient with a nonhealing chronic leg ulcer, present for more than 14 years despite several different local and systemic therapeutic modalities, represents a significant therapeutic challenge. We believe that the hypercoagulability status of this patient, which included β-thalassemia intermedia, heterozygocity for factor V Leiden and thrombocytosis, may contribute to the formation and perpetuation of the leg ulcer that was resistant to most of the treatments. Even the low-dose aspirin treatment that was indicated to prevent thrombotic complications due to thrombocytosis did not prevent development of the ulcer. A

successful response was obtained only after the combination therapy of intensive blood transfusions combined with hydroxyurea. Only following an increase in mean pre-transfusional hemoglobin levels above 9 and a reduction of fetal hemoglobin below 25% was improvement of peripheral tissue oxygenation achieved, followed by complete healing of the ulcer. Another beneficial role of regular blood transfusions combined with hydroxyurea therapy is the reduction of circulating abnormal red blood cells and amelioration of the hypercoagulable state.

Screening for thrombophilia should be considered in any patient with hemoglobinopathies and leg ulcers. The use of anticoagulant therapy in those cases warrants further investigation since only case reports have been published, not control-based studies.

Corresponding author:
Dr. C. Levin
Pediatric Hematology Unit, HaEmek Medical Center, Afula 18101, Israel
Phone: (972-4) 649-4189
Fax: (972-4) 649-5589
email: levin_c@clalit.org.il

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