Exchange blood transfusions for the treatment of leg ulcerations in thalassemia intermedia

Thalassemia intermedia is a heterogeneous, transfusion-independent form of β-thalassemia, with a clinical course dominated by multi-organ effects of chronic tissue hypoxia, in which hemoglobin F percentage seems to play an important role. We describe the case of a transfusion-independent thalassemia intermedia patient (total hemoglobin 10.7g/dL) with high hemoglobin F percentage (70%), who presented with persistent leg ulcerations. The patient was successfully treated with one-year exchange blood transfusions, which reduced hemoglobin F percentage to 35%.

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Thalassemia intermedia is a form of β-thalassemia characterized by later clinical onset with milder anemia, often permitting survival without regular transfusions, and longer life expectancy, compared to thalassemia major.[1] The disease is quite heterogeneous, both in terms of clinical presentation and of molecular defect and several different genotypes - homozygous, heterozygous and compound heterozygous - have been considered responsible.[1] The clinical course depends on hemoglobin and fetal hemoglobin levels, age of first symptoms, splenomegaly and expansion of ineffective hemopoiesis.[2] In most cases, the disease presents several complications which are mainly caused by chronic anemia and the resulting prolonged tissue hypoxia and include significant extramedullary hemopoiesis, hypersplenism, increased intestinal iron absorption, folic acid deficiency, thrombotic events, pulmonary hypertension and leg ulcers.[1-4] We report herein the case of a thalassemia intermedia patient with a hemoglobin (Hb) level of 10.7g/dL (with 70% HbF), who presented with persistent leg ulcerations and was successfully treated with exchange blood transfusions. This kind of therapy has not yet been applied in patients with thalassemia.

Case Report

A 21-year-old male patient with thalassemia intermedia was presented to our outpatient clinic with a 6-month history of leg ulcers that were refractory to conventional treatment. He had been transfused only occasionally until the age of 10, when he underwent splenectomy due to significant splenomegaly. Since then, his Hb level never dropped below 9.8 g/dL and the mean Hb level of the 2-year period preceding his admission was 10.4 g/dL. The patient was not a smoker.

The physical examination during his admission revealed a palpable liver 4.5 cm below right costal margin and a II/VI systolic ejection murmur over the cardiac apex and the fourth left intercostal space. There were two leg ulcers, a large one, measured 4×3 cm, on the right ankle and a smaller one, measured 3×2.5 cm, on the left ankle. The surrounding skin had a blue-purple discoloration with scaling and scarring; no signs of infection were present. The distal pulses of lower limbs were bilaterally palpable and Doppler examination of the arteries and veins was normal. No calcification was detected by X-ray in the tibial arteries. Finally, the wound cultures were negative.

Regarding the further patient evaluation, fundoscopy revealed the presence of angioid streaks. The ECG showed changes of left ventricular hypertrophy and the chest X-ray demonstrated a normal cardiac size, without clear presence of extramedullary erythropoietic masses. Echocardiography revealed left atrial and left ventricular enlargement, a moderate degree of mitral regurgitation and an increased cardiac output. The laboratory evaluation showed a total hemoglobin level of 10.7 g/dL, with 70% of HbF, an erythroblast count of 9,450/μL, a white cell count of 6,200/μL, a platelet count of 450,000/μL and a serum ferritin concentration of 305 mg/dL. Except for an increased indirect bilirubin level (4.5 mg/dL), the rest biochemistry profile was normal.

Due to his high hemoglobin level, the patient was considered a good candidate for exchange transfusions. He underwent this therapy once monthly, with 600 mL blood exchange each time. The leg ulcers were gradually improved and their area began to decrease. After six months, the ulcers were completely healed. The pretransfusion Hb level was reduced to 9.8g/dL, while the HbF dropped to 35%. The exchange transfusions were continued for a year in total, when the Hb level was 9.4g/dL. Since then, the patient started to be regularly transfused every 3 weeks with two packed red cell units and chelated with subcutaneous desferrioxamine at 30 mg/kg, four times a week.

At the last follow-up visit, one year later and 2 years after his initial presentation, the leg ulcers had not recurred and there were no signs of other dystrophic skin changes. His pretransfusional hemoglobin was maintained at a level higher than 9.2 g/dL, 30% of which was HbF and serum ferritin level was 750 ng/mL. Moreover, erythroblast count fell to 5,200/μL and platelet count to 375,000/μL.

Discussion

Dystrophic skin changes and leg ulcers are a well-known complication in hemoglobinopathies.[5] They occur in one third of young patients with untreated or poorly controlled thalassemia intermedia and constitute a considerable cause of chronic pain, disability and repulsive appearance.[5,6] In most cases, leg ulcers start as superficial lesions after minor trauma, insect bites, friction or scratches, and tend to expand rapidly.[5]

Poor oxygen delivery to the peripheral tissues represents the leading pathogenetic mechanism because of the resultant cutaneous ischemia.[4-6] Some adult thalassemia intermedia patients have quite low hemoglobin levels (6.0-6.5g/dL), although the average hemoglobin is above 7.0 g/dl in the majority of cases.[4] Apart from Hb level, Hb composition is also important for tissue oxygen delivery. Hemoglobin F percentage is remarkably variable among these patients, ranging between 5% and 100%.[4,6] Hemoglobin F shifts the hemoglobin-oxygen dissociation curve towards higher oxygen affinity, hence inducing a functional anemia that results to tissue hypoxia.[2] In addition, thalassemia intermedia patients have been found to have red blood cells with abnormal rheologic properties.[7] The reduced red cells deformability and their enhanced adherence to endothelial cells might contribute to thalassemia microcirculatory disorders.[5,7] Local infections and edema due to venous stasis and possibly right heart failure have also been implicated.[4,5] Furthermore, structural abnormalities of blood vessels are often present in thalassemia patients. Pseudoxantoma elasticum (PXE), a diffuse connective tissue disorder, has been described in such patients and its vascular manifestations are caused by degeneration of the elastic lamina of the arterial wall, often with calcium deposition.[8,9]

In the present case, it is of particular interest that leg

ulcers developed despite the high Hb levels. In the absence also of heart failure and clear local infection, the ulcers have to be attributed mainly to the high percentage of HbF, in coexistence with red cells deformities and PXE vessel abnormalities. Actually, the ocular manifestations of PXE, termed angioid streaks, were present in the described patient. The potential role of high HbF concentration in the development of dystrophic skin changes and subsequently leg ulcers has also previously been reported.[10]

Leg ulcers are slow and difficult to heal. Blood transfusions and short-term treatment with hydroxyurea or recombinant human erythropoietin have been shown to favor ulcer healing by ameliorating the degree of anemia, but in most cases the ulcers recur when therapy is discontinued.[4,5] Moreover, local application of platelet-derived wound healing factor and perilesional injections of granulocyte-macrophage colony-stimulating factor may be beneficial for chronic ulcers.[5,6] Avoidance of trauma and good care of minor lesions are also important in order to avoid further expansion.[5]

In the present case, the high Hb levels made the regular transfusion therapy problematic. The decision for exchange transfusion was based on the need for a fast reduction of Hb F level and avoidance, at the same time, of volume overload. Indeed, six months after the onset of treatment, the ulcers had been completely healed and Hb F had fallen to 35% of the total Hb level, which was 9.8 g/dL. Moreover, the ineffective hemopoiesis was further suppressed, due to the reduction of tissue hypoxia, and after one year of exchange transfusions the patient was in a position to receive regular transfusion therapy. One more years later and two years after his initial presentation, the pretransfusion total Hb level ranged above 9.2 g/dl and the percentage of HbF was 30%, while ulcers had not recurred. Therefore, it seems that HbF level plays an important role in tissue hypoxia in patients with hemoglobinopathies while exchange transfusions constitute an alternative therapy for leg ulcers suitable for cases with high Hb level and simultaneous high percentage of Hb F.

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