To the Editor:

We found the article by Koshy et al., entitled "Leg Ulcers in Patients With Sickle Cell Disease" very interesting. However, we want to make some comments mainly addressed to the factors implicated in the development of leg ulcers in sickle cell disease that, in our opinion, bring insights into the pathogenic mechanism of this complication. Among the contributing factors, the authors refer to "...the vessel obstruction by sickled cells, increased venous and capillary pressure, secondary bacterial infection, and decreased oxygen-carrying capacity of blood...", but they make no mention of the possible pathogenic role played by hemostatic abnormalities. In this regard, there are interesting reports, in both sickle cell disease and thalassemia syndromes, of vaso-occlusive microthrombotic events that, related to blood hypercoagulability, are responsible for the end organ damage frequently observed in these diseases. In corroboration with this view, we recently found indirect evidence that the leg ulcers may also be considered as a clinical equivalent of an end organ damage related to an in vivo chronic activation of blood coagulation. Indeed, in some adult subjects with sickle cell disease/β-thalassemia, complaining for long time of refractory leg ulcers, we detected the presence of an acquired antithrombin III deficiency, related to a chronic thrombin activation as expressed by an increase of plasma levels of fibrinopeptide A, along with increase of thrombin-anithrombin complex, D-dimer fragment, and fibrinogen/fibrin degradation products. When we corrected the antithrombin III deficiency state by human antithrombin III concentrate (ATIII; Immuno, Pisa, Italy) given in combination with subcutaneous calcium heparin (Calciparina; Italfarmaco, Milan, Italy), a complete healing of leg ulcers was observed after 6 weeks of treatment. It is also noteworthy that no recurrence of leg ulcers occurred in any of our patients at distance of 6 months from hATIII concentrate discontinuation.

On the basis of what was reported above, it would be interesting to know whether hemostatic profile was also considered in Koshy et al.'s cooperative study as among risk factors for leg ulcers, such as age, sex, type of sickle cell disease, hemoglobin level, fetal hemoglobin level, and body mass. This would be important for us because, contrary to Koshy et al's patients, ours were all affected by sickle cell disease/β-thalassemia, and the spontaneous raising and maintenance of leg ulcers was independent of hemoglobin concentration or fetal hemoglobin levels. We emphasize here that in Sicily, the coinheritance of sickle cell disease and β-thalassemia is much more frequent than the homozygous sickle cell disease. However, in our experience, the percent of patients with leg ulcers is comparable with that reported by Koshy et al.1

In conclusion, we believe that in hemoglobinopathic patients complaining of refractory leg ulcers and showing an acquired antithrombin III deficiency, replacement therapy with h-ATIII concentrate should be encouraged as an "aggressive treatment."

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REFERENCES


RESPONSE

Thank you for the two letters that were sent regarding our article, "Leg Ulcers in Patients With Sickle Cell Disease." The concept developed by Cacciola et al regarding hypercoagulability as a risk factor in sickle cell disease is interesting and needs further confirmation and detailed study. I would like to know how they measured the antithrombin III levels and whether functional immunologic assay was available. Why is the level of AT-III low? Is it due to thrombin activation or decreased production secondary to liver disease? If AT-III was low, then administration of AT-III could have a basis for therapy in patients with leg ulcers. It would be important to study hypercoagulable states and/or AT-III levels in all patients with sickle cell disease, ie, SS and SC, and to evaluate if results were the same in patients with and without leg ulcers. Therefore, further studies are needed before AT-III therapy is recommended. In our study, hypercoagulable states and AT-III levels were not studied.

In response to the letter from Moshe and Golan regarding the use of Omiderm (a temporary synthetic skin substitute) for healing of leg ulcers, several such topical techniques were used by the various participants in the study, and everyone reported success by the different agents. Therefore, Omiderm may be used as an alternative in patients with leg ulcers.

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Blood hypercoagulability as a risk factor for leg ulcers in sickle cell disease [letter; comment]

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