Anagrelide-Induced Relapse of a Hydroxyurea-Induced Leg Ulcer in a Patient With Primary Thrombocythemia

To the Editor: Patients receiving hydroxyurea have been reported to have development of painful leg ulcers, among other cutaneous side effects. Hydroxyurea-induced leg ulcers are usually painful, are difficult to treat, and require cessation of therapy. The use of anagrelide hydrochloride has substantially increased the therapeutic options for patients with myeloproliferative disorders associated with thrombocythemia. The therapeutic options for patients with primary thrombocythemia who require platelet-lowering agents include busulfan, human recombinant interferon, hydroxyurea, and anagrelide; of these options, anagrelide seems to be associated with the fewest side effects. Herein we describe a patient who had recurrence of a hydroxyurea-induced leg ulcer while taking anagrelide.

During an episode of gastrointestinal bleeding, a 74-year-old woman was discovered to have thrombocytosis (platelet count, 2,040 x 10⁹/L). A bone marrow aspirate and biopsy showed severe megakaryocytic hyperplasia. She was given hydroxyurea (1 g/day), and 5 months later, her platelet count had decreased to 511 x 10⁹/L. Subsequently, her treatment regimen was changed to human recombinant interferon alfa-2b, but intolerable side effects prompted reinstitution of hydroxyurea therapy (1 g/day). Fifteen months later, an extremely painful ulcer developed over the right lateral malleolus. Treatment with aspirin, pentoxifylline, leg elevation, and various topical wound dressings failed to heal the ulcer, which increased in size to 3 by 3.5 cm. Hydroxyurea treatment was discontinued 5 months later, when its association with the ulcer was identified. The ulcer healed over a 4-month period.

Three years later, the patient’s platelet count increased to 834 x 10⁹/L. Interferon therapy was reintroduced, but side effects again led to its discontinuation 1 month later. The patient was given anagrelide (1 g/day), and the platelet count promptly diminished to 186 x 10⁹/L. Five months after institution of anagrelide therapy, extreme pain developed over the right lateral malleolus, followed 2 weeks later by the appearance of an ulcer in the exact location of the previous hydroxyurea-induced lesion (Fig. 1).

Anagrelide has an excellent safety profile and, accordingly, is evolving as a first-line agent for myeloproliferative disorders associated with thrombocytopoiesis, including primary thrombocythemia. Side effects of this agent include headache, palpitations, diarrhea, and fluid retention and dermatologic side effects such as mild transient rash; hyperpigmentation in the lower extremities was reported in 4 of 577 patients. Hydroxyurea-induced leg ulcerations have been described in 14 of 115 patients; the pathogenesis is currently unknown but may be related to sustained damage to basal keratinocytes. These ulcers reappear when hydroxyurea therapy is resumed, but we are unaware of previous reports of leg ulcers recurring with administration of anagrelide. The possibility that the recurrence of leg ulcer in our patient was unrelated to treatment with anagrelide cannot be ruled out. Because many patients with thrombocytopoiesis are likely to have anagrelide substituted for treatments associated with more side effects, we would be interested to learn whether other physicians have noted this particular cutaneous side effect in hydroxyurea-treated patients who subsequently have received anagrelide therapy.

Guillermo J. Ruiz-Argüelles, M.D.
Centro de Hematología y Medicina Interna de Puebla and Laboratorios Clínicos de Puebla
Puebla, Mexico
Guillermo J. Ruiz-Delgado
Facultad Mexicana de Medicina de la Universidad La Salle
Mexico City, Mexico
Guillermo Ruiz-Reyes, M.D.
Laboratorios Clínicos de Puebla
Puebla, Mexico
Selbert G. Chernoff, M.D.
Lee’s Summit Physicians Group
Lee’s Summit, Missouri

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Fig. 1. Punctiform anagrelide-induced malleolar ulcer occurring in center of scar from previously healed hydroxyurea-induced lesion. Despite its small size, the ulcer was extremely painful.