

Leg ulcers associated with hydroxyurea therapy

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A 72 year-old woman with chronic myelogenous leukemia (CML) in first chronic phase received hydroxyurea (HU) because of intolerance to interferon. After two years of treatment with 1.5 g/day, she presented with two cutaneous ulcers in her right leg. The ulcers were extremely painful, with violaceous macules and edema surrounding them. No vascular disease could be ascertained in non-invasive studies. Analgesics, debridement, topical wound dressings and oral antibiotics were applied when necessary. After a dose decrease ulcers showed a tendency towards a slow resolution over a four month period.

Two months later, a rebound in leucocytosis and myelemia made it necessary to raise HU dose, and, subsequently, a new ulcer appeared in her left leg. HU was definitely withheld and replaced by busulfan.

Hydroxyurea (HU) is a hydroxylated derivative of urea used in the treatment of myeloproliferative disorders and acute myelogenous leukemia. Most side effects of HU are mild. Dermatological adverse effects are underestimated, since they are usually benign. These include alopecia, xerosis, diffuse hyperpigmentation, brown-nail discoloration, fixed drug eruption, stomatitis, acral erythema and scaling eruptions, photosensitization, skin tumours on UV-light exposed areas, dermatomyositis-like dermatitis, lichen planus-like dermatitis and painful ulcerations. The most common site of ulcers are legs, near the malleoli although they could be found over the tibia, in feet, and calves. The lesions use to appear after several months or years of maintenance therapy.

The pathogenesis remains poorly understood. The macroerythrocytosis which occurs in almost all patients taking hydroxyurea, may be a pathogenic factor because the megaloblastic erythrocytes circulate poorly through the capillary network. Similar leg ulcers have long been known to occur with certain hereditary blood dyscrasias, such as sickle cell anemia, thalassemia, and spherocytosis. In addition, HU causes cumulative toxicity on the basal layer of epidermis and produces cutaneous atrophy and impaired wound healing. Microvascular circulatory disturbance including erythromelalgia, Raynaud's phenomenon, digital ischemia, acrocyanosis, blue toe syndrome, livedo reticularis, cutaneous ulcers or necrotic purpura are common manifestations in myeloproliferative disorders. Finally, other factors such as poor microcirculation and



Figure 1.

peripheral edema, could be involved in certain patients.

Withdrawal of HU or a dose decrease may be enough to heal the ulcers. Successful treatment has been achieved occasionally with prostaglandin E1, pentoxifylline, topical GM-CSF, split-thickness skin grafting or apligraf.

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