Hydroxyurea引起之對稱性下肢潰瘍

—病例報告—

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Hydroxyurea-induced Symmetrical Lower Leg Ulcers

—A Case Report—

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Hydroxyurea is commonly used to treat chronic myeloproliferative disorders. Lower leg ulcer is a recently identified cutaneous adverse effect of long-term hydroxyurea therapy. We present a case of symmetrical painful lateral malleolar ulcers in a polycythemia vera patient who had been treated with hydroxyurea for 6 years. Histologically, the ulcer showed diffuse dermal fibrosis without vasculitis. The ulcer was recalcitrant despite topical treatment, but it resolved completely in one month after hydroxyurea was discontinued. Hydroxyurea-induced lower leg ulcer is a unique clinical entity that necessitates early recognition and prompt discontinuation of hydroxyurea. (Dermatol Sinica 19：249-254, 2001)

Key words: Hydroxyurea, Leg ulcer

Hydroxyurea常用在治療慢性骨髓增生性疾病。下肢潰瘍近來才確定爲長期使用hydroxyurea後在皮膚所造成的副作用。我們報告一例使用hydroxyurea治療眞性紅血球增生症六年後引起的對稱性雙側外側足踝潰瘍。組織學下此潰瘍呈現廣泛性眞皮纖維化且無血管炎。局部治療對此潰瘍無效，但在病人在停用hydroxyurea一個月後潰瘍完全癒合。Hydroxyurea引起之下肢潰瘍爲一特殊的臨床表現，必須早期確認並馬上停用hydroxyurea。(中華皮誌19：249-254, 2001)

INTRODUCTION

Lower leg ulcer is a recently identified cutaneous adverse effect of long-term hydroxyurea therapy.[1-8] It is extremely painful and typically located close to malleoli. Unless hydroxyurea is discontinued, the ulcer is recalcitrant to therapy. We report a 68-year-old man with typical manifestations of hydroxyurea-

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induced lower leg ulcers.

CASE REPORT

A 68-year-old Taiwanese man visited us for evaluation of a painful ulcer of one month's duration over left lateral malleolus in August 1998. He had a history of polycythemia vera of 14 years' duration and had been treated with hydroxyurea for 6 years. He took aspirin, coumadin, and hydroxyurea (1500mg per day) for the polycythemia vera at that time. He also had hypertension and atrial fibrillation under the medication of digoxin and diltiazem. He reported no trauma to the left lateral malleolar area prior to the development of the ulcer. Physical examination revealed an irregular-shaped shallow ulcer measuring 2 by 2.5 cm over the left lateral malleolus. It was extremely painful and tender to touch. His peripheral pulses were normal and there was no varicose vein in his legs. His complete blood counts showed: white blood cells 12.01 K/ μ l, red blood cells 4.75 M/ μ l, hemoglobin 15.2 g/dl, hemotocrit 47.6%, MCV 100.2 fl, and platelets 574 K/ μ l. A 4-week course of oral antibiotics and topical dressings was given, but in vain. The ulcer persisted and remained very painful. Tissue culture yielded no bacteria. A biopsy taken from the ulcer showed diffuse dermal fibrosis with sparse perivascular mononuclear cell infiltration (Fig. 1). There were no lobular aggregates of plump, thickened capillaries and venules in the dermis. Debridement with a rotational flap was performed in September 1999. An ulcer developed due to poor wound healing. Afterwards, the ulcer was treated with topical antibiotics and occlusive dressings. Complete reepithelialization was achieved in late December 1999.

On April 24, 2000, he visited us for evaluation of a painful erythematous swelling over his right lateral malleolus of one week's duration. Examination revealed a palm-sized erythematous swelling plaque over the right lateral malleolus, diffuse hyperpigmentation of his face and brownish discoloration of his nails. His complete blood counts showed: white blood cells 13.62 K/ μ l, red blood cells 3.5 M/ μ l, hemoglobin 13.2 g/dl, hemotocrit 41.9 %, MCV 119.7fL, and platelets 671 K/ μ L. Under the impression of cellulitis, he was admitted. Despite bed rest with lower leg elevation and intravenous antibiotics, the lesion aggravated during the initial 10 days following admission. A bulla developed at the center of the plaque. The lesion was extremely painful and tender to touch. The bulla ruptured and a dendritic shallow ulcer with serous discharge developed in the center of the plaque. Several small irregular-shaped bullae developed around the malleolar ulcer and resulted in several shallow ulcers (Fig. 2). Repeated tissue cultures for bacteria, fungus and mycobacterium were not revealing. Blood cultures were also yieldless. He was discharged on May 16, 2000. Topical antibiotics and occlusive therapy were given with poor response. According to his clinical and pathological presentations, hydroxyurea-induced lower leg ulcer was impressed. Hydroxyurea was not discontinued until July 28, 2000 when busulfan and anagrelide, purchased by the

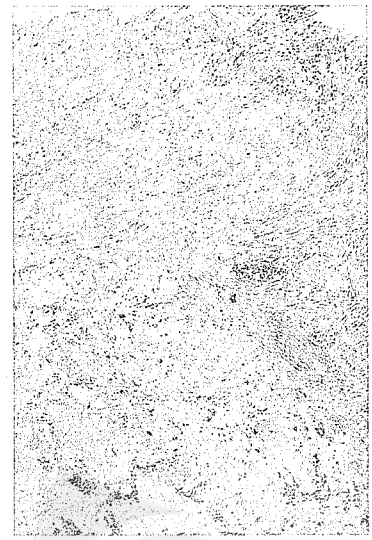

Fig. 1
There was diffuse dermal fibrosis with sparse perivascular mononuclear cell infiltration. (H & E x40)

patient himself from the United States, were used for polycythemia vera. The ulcer dramatically resolved in one month after hydroxyurea was discontinued (Fig. 3).

DISCUSSION

Hydroxyurea is the drug of choice for treatment of a variety of chronic myeloproliferative disorders. It has been used for almost 40 years.[9] In dermatology, hydroxyurea was initially used for psoriasis.[10] It binds to the M2 protein of the ribonucleotide reductase, inhibiting DNA synthesis during S phase of cellular proliferation.[11] Cells in the S phase of the cell cycle are hence killed selectively.

Hydroxyurea is usually well tolerated. The most common hematological adverse effects are megaloblastic changes of erythrocytes that occur in almost all patients treated with hydroxyurea.[12] Documented dermatological adverse effects of hydroxyurea include stomatitis, oral ulcers, xerosis, alopecia, diffuse hyperpigmentation, brown discoloration of nails, and a

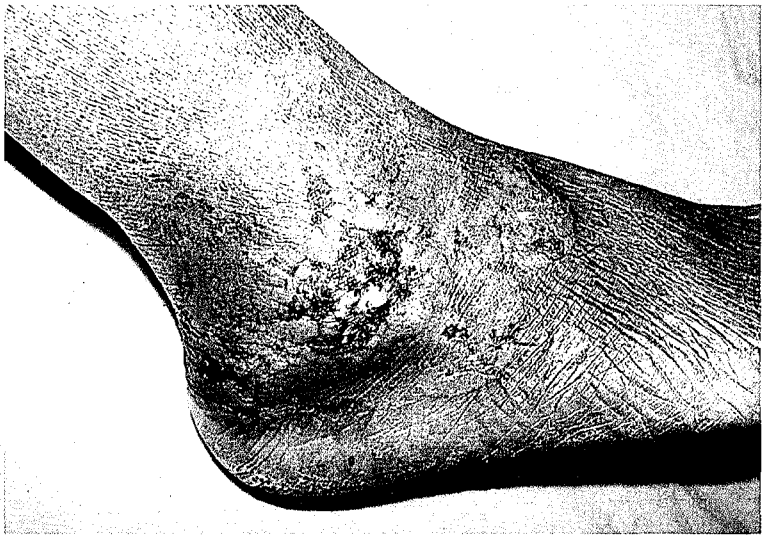

Fig. 2
There were multiple small irregular-shaped shallow ulcers on an erythematous swelling base around a dendritic malleolar ulcer.

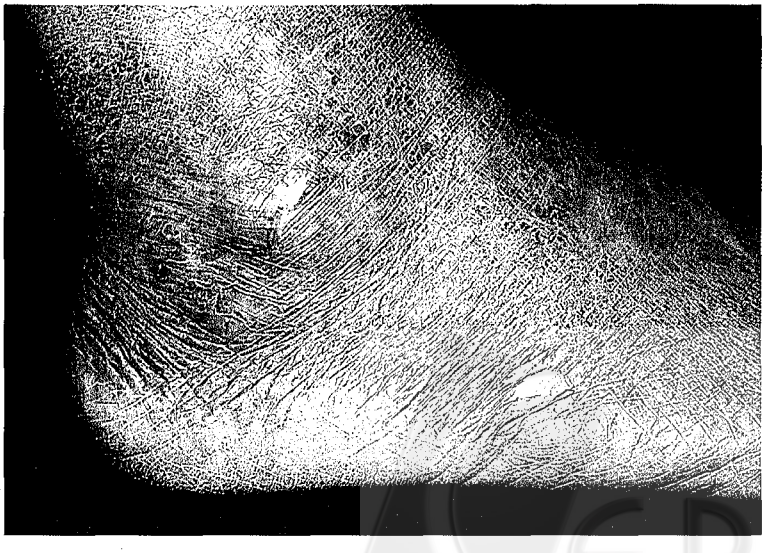

Fig. 3
The ulcer resolved completely in one month after discontinuation of hydroxyurea.

dermatomyositis-like eruption.[13-17] In 1986, Montefusco first reported the association of lower leg ulcer with hydroxyurea therapy.[1] He described 17 patients (8.5 percent) who experienced lower leg ulcers located mainly at malleolar areas (16 of 17) among 200 patients with long-term hydroxyurea therapy for chronic myelogenous leukemia.[1] Several cases were reported afterwards.[2-6] Recently, two retrospective studies described the features of hydroxyurea-induced leg ulcers.[7,8]

Hydroxyurea-induced leg ulcers usually develop in patients with long-term hydroxyurea therapy. In two studies, the mean duration of hydroxyurea therapy is 5 and 6.1 years respectively.[7,8] The mean cumulative dose of hydroxyurea is 3.21 kg.[7] About 60 percent of the patients have multiple ulcers.[7-8] The ulcers are typically located close to malleoli, and also develop in tibial area, calves, dorsal aspects of feet and toes. They are usually extremely painful. Other cutaneous adverse effects of hydroxyurea, including a dermatomyositis-like eruption, brown discoloration of nails, diffuse hyperpigmentation, and cutaneous atrophy, can be identified in about 60 percent of the patients with leg ulcers.[8] In our patient, he also has brown discoloration of nails and diffuse hyperpigmentation. His cumulative hydroxyurea dose was about 3kg when the first lower leg ulcer developed. The histological findings of the ulcers are non-specific, including epidermal atrophy, dermal fibrosis and scar tissue without vascular lesions.[1,3,7,8]

The ulcers are usually recalcitrant to various treatment modalities unless hydroxyurea is discontinued.[1,7,8] Complete healing or significant improvement of the ulcers can be expected only after hydroxyurea is discontinued.[7,8] If hydroxyurea is restarted, ulcers may recur.[7]

However, the ulcers may sometimes resolve with conservative therapy while hydroxyurea therapy continues.[2,5] Kido *et al.* used intravenous PGE_1 and oral pentoxifylline for a patient with hydroxyurea-induced lower leg ulcers while continuing hydroxyurea.[5] The ulcers were almost completely healed in 4 weeks. Nguyen and Margolis employed conservative therapy including manual debridement, topical antibiotics, and occlusive dressing for four patients without discontinuing hydroxyurea.[2] Four of the 6 ulcers slowly resolved. Our patient underwent debridement with a rotational flap for the left malleolar ulcer. An ulcer developed due to poor wound healing. The ulcer completely resolved after a 3-month course of topical antibiotics and occlusive dressings while hydroxyurea was continued.

The mechanism of hydroxyurea-induced ulcer is not clear. There are no major vascular disease that can account for the chronic recalcitrant ulcers in these patients.[1-8] Nguyen and Margolis proposed that cutaneous atrophy induced by hydroxyurea was prone to minor trauma.[2] The antimetabolite effect of hydroxyurea delayed wound healing, resulting in a chronic ulcer. Sirieix *et al.* proposed that impaired cutaneous microcirculation caused by hydroxyurea-induced reduction of red blood cell susceptibility to deformation, followed by minor trauma, could lead to cutaneous ulceration.[8]

Hydroxyurea-induced lower leg ulcer should be differentiated from livedoid vasculitis which is also typically located at lower legs and feet and very painful. Livedoid vasculitis is preceded by purpuric macules and papules that are not seen in hydroxyurea-induced ulcers.[18] Besides, prominent deposition of fibrinoid material in dermal vessels can usually be revealed in livedoid vasculitis.[18] Stasis ulcer is usually accompanied by varicose veins and not so painful as hydroxyurea-induced ulcers.

Hydroxyurea was approved and introduced for chronic myeloproliferative diseases in Taiwan in 1989.[19] The daily dose for chronic myeloproliferative disorders ranges from 20 to 30mg/kg per day. Interferon α and busulfan are alternatives, but side effects are more significant.[20-22] Inteferon α should be administered subcutaneously three times a week and has side effects such as flu-like syndrome,

fatigue, anorexia and weight loss.[22] Busulfan is less effective in suppressing erythropoiesis and may cause pulmonary fibrosis after long-term use of this drug.[24] Besides, its suppression of white blood cells and platelet counts may be unpredictable and prolonged.[24] Anagrelide is a newly developed drug for myeloproliferative disease, especially for essential thrombocythemia.[22,23] It is a reasonable alternative for patients who do not tolerate hydroxyurea.[22,23] The adverse effect of anagrelide is related mainly to the its vasodilatory and inotropic effects, including headache and palpitation.[22,23]

On average, the mean duration of hydroxyurea therapy before the development of lower leg ulcers is 5 to 6 years.[7,8] About 8.5 to 12.2 percent of patients under long-term hydroxyurea therapy develop hydroxyurea-induced leg ulcers.[1,7] However, to our knowledge, hydroxyurea-induced lower leg ulcers have not been reported in Taiwan. It may be due to the racial difference. However, it is also possible that physicians in Taiwan are not aware of this unique clinical entity, and hence this adverse effect of hydroxyurea is not reported. Hydroxyurea-induced lower leg ulcers should be suspected in patients with unexplained extremely painful malleolar ulcers who are under long-term hydroxyurea therapy. If an alternative therapy is feasible, hydroxyurea should be promptly discontinued.

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