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CASE REPORT

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Severe skin ulceration associated with Wegener's granulomatosis: successful treatment with hyperbaric oxygen and prostaglandin E_1

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Abstract A 36-year-old woman patient with intractable skin ulcers associated with Wegener's granulomatosis was successfully cured by combination therapy with hyperbaric oxygenation therapy (HBO) and intravenous prostaglandin E_1 (PGE_1). Treatment for 4 months with prednisolone, intravenous PGE_1, and cyclophosphamide did not result in healing of the multiple skin lesions on her legs. Repeated HBO with intravenous PGE_1 therapy over 6 months resulted in a complete healing of the skin ulcers. We recommend the use of HBO combined with PGE_1 for severe cutaneous lesions associated with generalized vasculitis.

Key words Hyperbaric oxygen therapy (HBO) · Skin ulcer · Wegener's granulomatosis (WG)

Introduction

Wegener's granulomatosis (WG) is part of the spectrum of systemic vasculitis, and is a clinicopathological syndrome involving the upper and lower respiratory tracts, kidneys, and less commonly the eyes, joints, skin, and neural tissues. First described by F. Wegener in 1936, necrotizing granulomatous vasculitis is limited to the lower respiratory tract, while focal segmental glomerulonephritis and small-vessel or granulomatous vasculitis occurs in other tissues. Cutaneous manifestations occur at any time in 46% to 50% of patients with WG, and typically include palpable purpura, predominantly in the lower extremities. Vesicles, necrotic papules, lesions, subcutaneous nodules, and petechiae have been described.[1,2]

We present a case of intractable skin ulcers in a patient with WG. The patient received hyperbaric oxygenation therapy (HBO) combined with intravenous prostaglandin E_1 (PGE_1), which resulted in healing and scarring of the skin ulcers within 6 months. We discuss the probable mechanisms of the combination therapy with HBO and intravenous PGE_1.

Case report

The patient was a 36-year-old Japanese woman who developed nasal bleeding and was noted to have a tumor in the left orbit in 1978. In 1984, she was diagnosed with Wegener's granulomatosis based on the presence of left orbital tumor, saddle nose, nasal bleeding, hearing loss, skin ulcers, and the histopathological findings from a nasal mucosa biopsy. She was then treated with prednisolone (30 mg/day) and picibanil (5 KE/week). In January 1994, erythema and a subcutaneous nodule with tenderness appeared on the right pretibial skin. A skin biopsy taken from the erythema showed inflammatory granulomatous changes, indicating features compatible with WG. She developed skin ulceration with circumferential cellulites and bacterial infection, and the ulcers gradually enlarged on the left foot. Similar ulcers also appeared on her left knee and her right hand. The patient was admitted to the local hospital for treatment of the skin ulcers in August 1994. However, she did not respond satisfactorily to the prednisolone and cyclophosphamide (75 mg/day) with intravenous PGE_1 in September, and she was transferred to our hospital in October 1994.

Physical examinations on admission showed purpura in both upper limbs, swelling of the lower extremities, cutis reticularis in both legs, and a subcutaneous nodule measuring 6 cm × 4.5 cm in the medial aspect of the left thigh. Furthermore, a rodent ulcer with marginal cellulitis was observed on the dorsum of the right hand. Six similar ulcers

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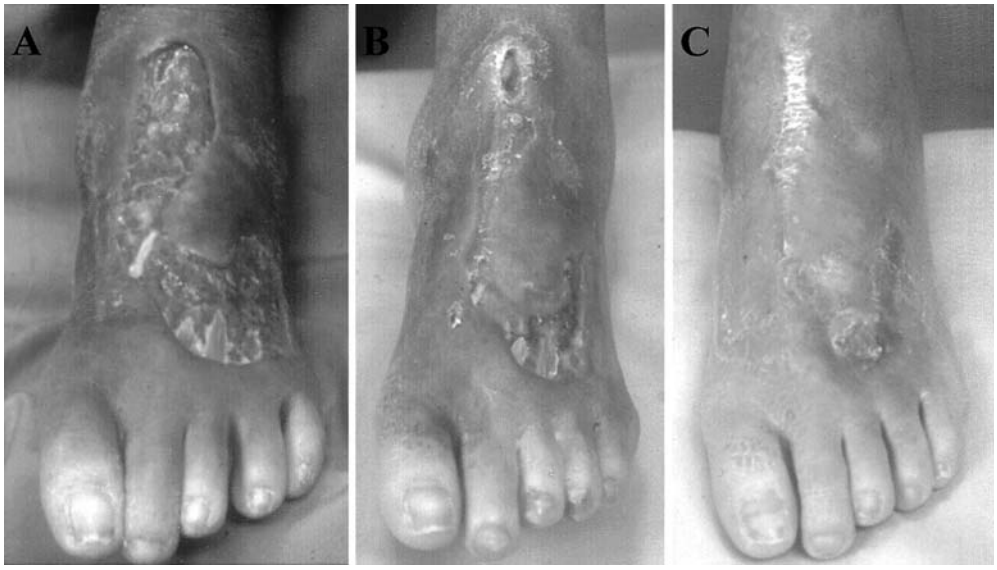

Fig. 1. **A** Photograph taken on admission showing a rodent ulcer measuring 10 cm × 7 cm on the left foot, with exposure of the tendon in the ulcer floor. The patient received combination therapy of HBO with intravenous PGE_1 at 120 μg/day. **B** Photograph taken after the completion of 30 sessions of HBO. Ulcer pain, bleeding, and infection had completely disappeared, with initiation of the healing process and the formation of granulation tissue. **C** Photograph taken after the completion of 112 sessions of HBO. Note the complete healing and skin scarring

were noted over the left foot, with the largest hoot type ulcer located on the dorsum of the left foot and measuring 10 cm × 7 cm, which resulted in exposure of the tendon in the ulcer (Fig. 1A). Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from these ulcers. A neurological examination revealed mild paresthesia and hypesthesia on ankle jerks to both feet.

Laboratory studies on admission showed a hemoglobin level of 10.5 g/dl, a platelet count of 27.8×10^4 /μl, and evidence of systemic inflammation, with peripheral leukocytosis (10200 cells/μl) and an increased proportion of leukocytes with segmented nuclei, a high erythrocyte sedimentation rate (113 mm/h), and elevated C-reactive protein level (15.6 mg/dl). Urinalysis did not show proteinuria. The concentrations of serum transaminase, lactate dehydrogenase (LDH) (313 IU/l), creatine kinase (CK) (55 IU/l), blood urea nitrogen (BUN) (19 mg/dl), and serum creatinine were within normal limits. Her total serum cholesterol value was normal at 149 mg/dl, but her triglyceride value was slightly elevated at 167 mg/dl. Total serum protein value was normal at 7.5 g/dl, but the serum albumin value was low at 3.8 g/dl. Electrophoresis showed slight hypogammaglobulinemia (12.7%), IgG of 719 mg/dl, IgA of 296 mg/dl, and IgM of 153 mg/dl. The complement levels were normal (C_3, 86 mg/dl; C_4, 37 mg/dl; CH_{50}, 65 U/ml), and the cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA) was negative. Partial thromboplastin time (PT) was normal at 12.0 s (control 11.7 s), a prolonged activated partial thromboplastin time (APTT) was normal at 25.3 s (control 31.4 s), fibrinogen was elevated at 762 mg/dl, and fibrin degradation product (D-dimmer) was elevated at 1.5 μg/ml. A chest X-ray demonstrated mild cardiomegaly with a cardio-thoracic ratio of 56%, and pulmonary fibrosis in the lower lobes of both lungs. Computed tomography (CT) showed the loss of the nasal septum and soft tissue filling in both orbital cavities and nasal sinuses.

The findings of sinusitis, eye, and cutaneous symptoms, and the pathological findings of necrotizing granulomatous vasculitis at skin biopsy, were compatible with the diagnosis of WG according to the 1990 criteria of the American College of Rheumatology.[3] To evaluate disease activity, another skin biopsy was taken from the hoot-type ulcer on the dorsum of the left foot, and showed multinucleated giant cells and palisading epithelioid cells, but neither leukocytoclastic vasculitis nor active extra vascular necrosis was found. Accordingly, we concluded that the skin ulcers had worsened and become enlarged by local ischemia caused by the chronic granulomatous changes. Although various antibiotics administrated for severe phlegmon resulted in the eradication of bacterial infection of the skin lesions, the skin ulcers still remained.

Therefore, the combination therapy of HBO and intravenous PGE_1 (120 μg/day) was applied to treat the refractory skin ulcers. HBO involved intermittent inhalation of 100% oxygen under 2.5 atmospheric pressure absolute (ATA) for 60 min, once a day, in a hyperbaric chamber, with the simultaneous infusion of PGE_1. We did not administer the oral PGE_1 pharmaceutical drug or antiplatelet coagulation therapy in order to clarify the benefit of intravenous PGE_1. The above treatment resulted in the appearance of granulation tissue, and reduced the pain associated with the ulcers after the completion of ten sessions of HBO. Skin grafting was not considered owing to the possible rejection of the transplanted skin as a result of poor development of new blood vessels and infection. At the end of the 30th session of HBO, the pain had completely disappeared and complete healing of the ulcer with an elimination of infection was noted, together with formation of granulation tissue (Fig. 1B). The aforementioned treatment was continued, and after 112 sessions the skin ulcers had completely disappeared and been replaced with scar tissue (Fig. 1C). At the last follow-up examination, conducted 7 years after discharge from our hospital, the patient was in a good general condition, and no recurrence of the skin ulcer was noted.

Discussion

WG is a complex disease that can be diagnosed by the presence of the classic triad of necrotizing granuloma of the respiratory tract, generalized vasculitis, and glomerulitis. The clinical manifestations in WG also include papulae, skin ulcers, and other secondary skin lesions such as infection. Camille et al.[4] reported 75 cases of patients with WG, and skin or mucosal involvement was noted in 35 patients. These included palpable purpura ($n = 26$), skin ulcers ($n = 5$), and necrotic papula ($n = 5$), and 47% of their patients demonstrated characteristic histopathological findings, including necrotizing vasculitis, granulomatous vasculitis, and palisading granuloma. Brons et al.[5] demonstrated the presence of IgG and/or IgA containing immune deposits in the subepidermal blood vessels in skin biopsies taken at initial presentation and at the onset of relapses from patients with WG, and suggested that immune complexes may trigger vasculitic lesions in WG. Patients with leukocytoclastic vasculitis also exhibit a rapidly progressive and widespread WG, whose general condition usually worsens with the development of severe arthritis, nephritis, and WG-related skin lesions.

We decided to use the combination therapy of HBO together with intravenous administration of PGE_1. This treatment was successful in healing the intractable skin ulcers. No serious adverse effects were identified. A combination of corticosteroids and cyclophosphamide is the standard therapy for WG, and results in long-term remission in 75% of WG cases. However, some patients have intractable skin ulcers, even though they have been treated with cyclophosphamide, corticosteroid, methotrexate, cyclosporin, and antibiotics.[4] In our case, the skin ulcers did not heal even though the patient was treated with the standard therapy and intravenous PGE_1. We considered that the main factor involved in severe skin ulcers was persistent local hypoxia resulting from chronic inflammation due to WG, and we believed that an improvement in the local hypoxia would be an important part of her treatment. We therefore decided to use a combination therapy of HBO with the intravenous administration of PGE_1. This is the first report that demonstrates the efficacy of this combination therapy for intractable skin ulcers in patients with WG.

HBO is widely used as a treatment for decompression sickness, and peripheral circulation incompetence causing skin ulcers in patients with diabetes and chronic occlusive arterial diseases, as well as in patients with cerebral palsy, ischemic brain disease, systemic sclerosis, rheumatoid arthritis, vasculitis, entero-Behçet syndrome, toxic megacolon, and irradiation-related complications.[6–14] The most important mechanism of the action of HBO in relation to the improvement of skin ulcers is thought to be a rise in tissue oxygen concentration. The correction of local tissue hypoxia in the damaged tissue results in fibroblast, epithelial cell, and interstitial cell resuscitation and proliferation. Furthermore, Fischer[8] reported that HBO resulted in a prompt arrest of bacterial growth and the formation of an epithelial cell layer. HBO also facilitates the anti-inflammatory response through the activation of superoxide dismutase (SOD), one of the biophylaxis mechanisms, which in turn increases the superoxide level.[15–17] We also reported that HBO exposure resulted in the suppression of the development of autoimmune symptoms such as proteinuria, facial erythema, and lymphadenopathy in MRL/lpr mice.[18,19]

PGE_1 has a powerful angiotelectasia action and inhibits platelet aggregation. Basically, although the regional blood flow is reduced under the high tissue oxygen levels during HBO, the vasodilatory action of PGE_1 on the vessels compensates for the disadvantages of HBO.[20,21] Furthermore, PGE_1 is thought to continue to maintain a relatively high partial pressure of oxygen over a longer time after treatment with HBO.[22] Thus, there appears to be a synergistic effect between HBO and PGE_1 therapy for refractory skin lesions.

Taken together, although further studies in WG patients with skin manifestations are necessary to establish the most effective dose of HBO and PGE_1, the duration of the treatment, and the route of administration of PGE_1, we recommend the use of HBO combined with PGE_1 for severe cutaneous lesions associated with serious hypoxia due to vasculitis syndrome such as WG.

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