Geriatrics Gerontology International

DOI: 10.1111/ggi.14546

LETTERS TO THE EDITOR

CASE REPORTS

Case of Werner syndrome with significant improvement of refractory skin ulcer despite fibroblast cellular senescence

Keywords: diabetes mellitus, atherosclerosis/fat metabolism, infectious disease, skin ulcer, Werner syndrome.

Dear Editor,

Werner syndrome (WS) is a hereditary premature aging syndrome with an estimated 700–2000 cases in Japan. It is inherited as an autosomal recessive trait, and causes graying of hair, juvenile cataracts, insulin-resistant diabetes mellitus, dyslipidemia, abdominal adiposity, atherosclerosis and malignant neoplasms in patients aged in their 30s to 50s. The cause of WS is a mutation in the *WRN* gene, a RECQ helicase on chromosome 8. Among patients with WS, 67.5% experience intractable skin ulcers, which are often accompanied by severe pain and osteomyelitis, and 15% of WS patients require amputation of the lower extremities.[1] One of the causes of intractable skin ulcers is the cellular senescence of fibroblasts, which lose their proliferation capacity and express inflammatory cytokines called senescence associated secretary phenotype. Although cellular senescence itself is untreatable, the negative effects of cellular senescence might be overcome by dealing with other factors involved in ulcers. Here, we report a case of a WS patient with intractable skin ulcers and cellular senescence of fibroblasts, who was able to avoid amputation by intensive treatment.

A 48-year-old woman with WS presented with intractable ulcers. She developed bilateral cataracts at the age of 32 years, and hair loss at 44 years. For 13 months, she had multiple ulcers on her left foot, which did not resolve despite visits to several dermatologists. A bird-like face and a high-pitched hoarse voice were also detected.

Her height was 148.8 cm, weight 43.4 kg and body mass index 19.8. She had a large 5 × 3-cm ulcer on the dorsum of her left foot that reached the periosteum, with a red granulation in the center and yellow necrotic tissue around it. No bleeding was observed. A 3 × 3-cm ulcer was also found in the left Achilles tendon area, exposing necrotic tendon tissue. Both ulcers were infected (Fig. 1a). She was diagnosed with diabetes, with a glycated hemoglobin of 6.7% and fasting blood glucose of 144 mg/dL. Her C-reactive protein was 6.44 mg/dL, and magnetic resonance imaging showed a sign of osteomyelitis (Fig. 1g). X-rays showed the calcification of the bilateral Achilles tendons (Fig. 1h). The cardio-ankle vascular index, ankle brachial index and skin blood flow were normal. Computed tomography showed 108 cm^2 of visceral fat accumulation. Her homeostasis model assessment of insulin resistance was 3.3, and the hyperinsulinemic euglycemic glucose clamp test (insulin infusion rate 1.25 mU/kg/min) showed that the patient's glucose infusion rate was 4.4 mg/kg/min (normal 9.43 ± 4.69), indicating insulin resistance. In addition, the skeletal muscle mass index was 4.68 kg/m^2 (normal >5.46).

According to the Japanese criteria for the diagnosis of WS, a definite diagnosis of WS was made. Genetic analysis showed that she had compound heterozygous mutations, the type 4 mutation, c.3139-1G>C and the type 1 mutation, c.3913 >T of the *WRN* gene.

Debridement of the wound, intravenous antimicrobial infusion and hyperbaric oxygenation were carried out. After negative pressure closure therapy, skin transplantation was performed from healthy femoral groin to the ulcers. These multidisciplinary treatments resulted in significant improvement of the ulcer (Fig. 1a-f).

We cultured skin fibroblasts from the wound area with the patient's consent (#1145, Chiba University Ethics Committee), and found that the proliferation of patient-derived dermal fibroblasts was slower than that of healthy individuals (data not shown). In addition, senescence-associated β-galactosidase staining showed strong cellular senescence (Fig. 1i,j). Fibroblasts from the WS patient showed increased mRNA expression of the aging marker, *CDKN1A*, the senescence-associated secretary phenotype factors *IL1B* and *IL6*. The nuclear protein LMNB1 was severely decreased (Fig. 1k). Taken together the patient's fibroblast showed severe cellular senescence. The datasets are available from the corresponding author on reasonable request.

Fibroblasts in WS show cellular senescence with decreased proliferation, increased senescence markers as seen in this case. Recently, we reported that WS fibroblasts have distinct characteristics between the trunk and the extremities, and that peripheral fibroblasts retain their osteogenic potential, while their adipogenic potential is reduced.[2] In addition, WS fibroblasts show overexpression of Pit1, a phosphorus transporter, and are prone to ectopic calcification.[3] In other words, senescent fibroblasts are prone to develop calcification, cause inflammation, leading to ulcer formation.

Risk factors for diabetic skin ulcers, representative skin ulcers in healthy individuals, include severe neuropathy, history of foot ulcers, peripheral artery disease, depression and poor glycemic control.[4] Sarcopenia and reduction of blood flow is also a risk factor for skin ulceration.[5-7] Therefore, along with cellular senescence of fibroblasts, atherosclerosis or poor diabetes control might contribute to the refractoriness of skin ulcers in WS through reduction of blood flow and susceptibility to infection. In the present case, fortunately, none of these factors were observed. These facts suggest that even in the presence of cellular senescence and senescence associated-secretary phenotype, if structural changes, such as fibrosis and atherosclerosis, are mild, wound healing of WS patients can be expected. Therefore, the present case implicated the importance of early diagnosis and early treatment of skin complications of WS patients.

Acknowledgement

We thank Ms Aki Watanabe for her excellent technical assistance.

DK and HK are contributed equally to this case report.

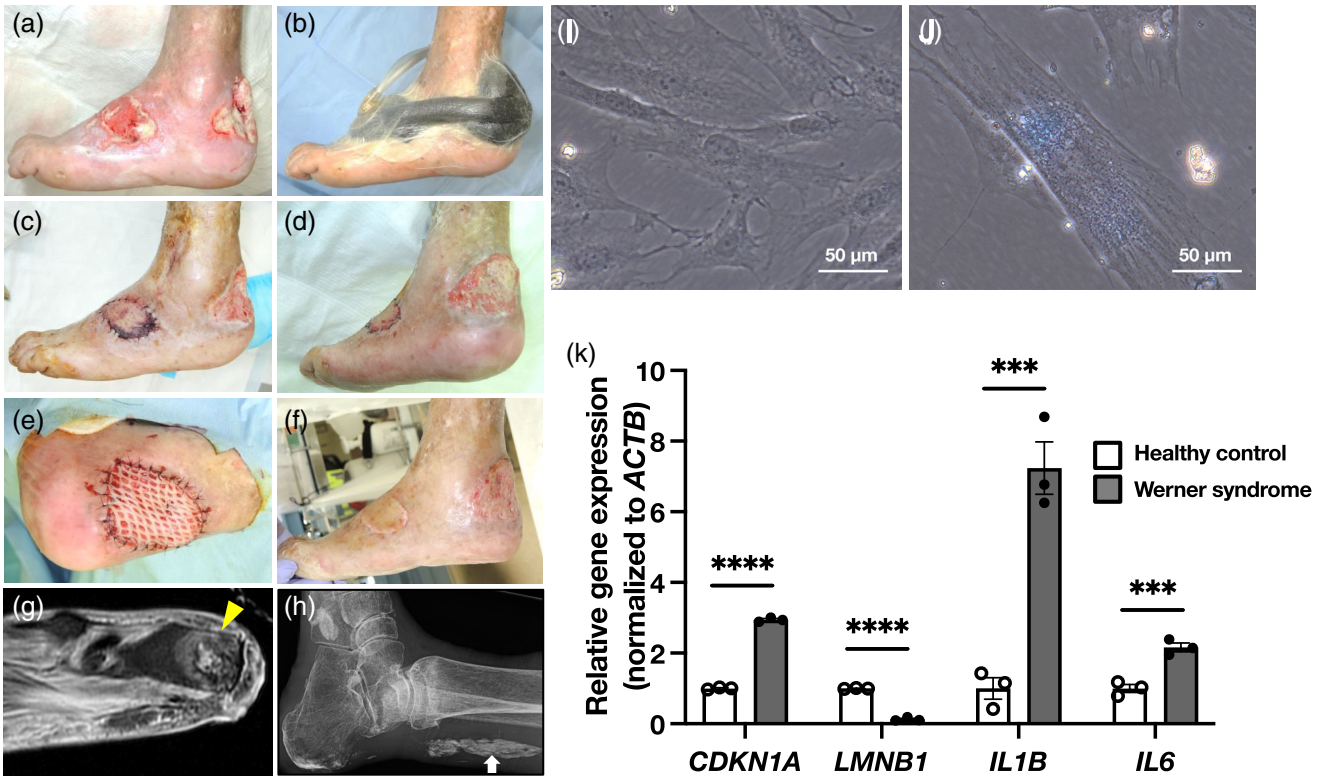

Figure 1 (a–f) The treatment of intractable skin ulcer. Hyperbaric oxygen therapy was used for 2 h at two atmospheres over 30 sessions for 68 days. Negative pressure closure therapy was used for 48 days using the V.A.C. ULTA Therapy System (KCI USA, Henderson, NE, USA). For the first 28 days, negative pressure of −75 mmHg was applied for 3 h and 30 min after immersion in 30 mL of saline for 10 min. For the second 20 days, negative pressure was applied alternately at −25 mmHg for 3 min and at −75 mmHg for 3 min. (g) Magnetic resonance imaging showing high intensity on Short tau inversion recovery (STIR), indicating osteomyelitis. (h) Achilles tendon calcification typical for Werner syndrome (WS). (i, j) Senescence-associated β-galactosidase staining of (i) normal and (j) WS fibroblasts. Normal fibroblasts were collected from a forearm of an individual without WS and without obvious chronic diseases. (k) Real-time reverse transcription polymerase chain reaction analysis using the fibroblasts from the WS patient and healthy control, showing cellular senescence. White bar: healthy control, gray bar: Werner syndrome. ***$P < 0.001$, ****$P < 0.0001$.

Disclosure statement

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Kinoshita D, Kato H, Kaneko H, et al. Case of Werner syndrome with significant improvement of refractory skin ulcer despite fibroblast cellular senescence. Geriatr. Gerontol. Int. 2023;23:239–241. https://doi.org/10.1111/ggi.14546

Omicron variant infections and multiple strokes in older adults

Keywords: elderly, multiple strokes, omicron variant.

Dear Editor,

Ischemic stroke is a major complication of coronavirus infection 2019 (COVID-19).[1] Among strokes, multiple strokes, including bihemispheric cerebral infarctions, are uncommon, suggesting an embolic source, and are associated with increased death and disability.[2] During the seventh wave of the COVID-19 pandemic in Japan, >200 000 people a day were infected with the omicron variant. During this period, multiple strokes with poor prognosis occurred frequently in older people.

A 92-year-old woman was infected with the omicron variant due to a cluster outbreak at the facility she lived in. She had already received the third dose of the COVID-19 mRNA vaccine. She had a fever of 38°C, loss of appetite, decreased sense of smell and polymerase chain reaction testing confirmed COVID-19 infection. Chest radiographs showed no evidence of pneumonia. Considering the patient's advanced age, she received intravenous infusion of remdesivir as antiviral therapy, 200 mg on the first day, and 100 mg on and after the second day, once a day for a total of 5 days. With systemic management, COVID-19 infection did not become severe and her appetite recovered within a week. However, 2 weeks after the COVID-19 infection, she suddenly developed a loss of consciousness. Magnetic resonance imaging of the head showed swollen cerebellar hemispheres and high-intensity lesions in the bilateral cerebellum and right occipital to parietal lobes on diffusion-weighted images, leading to a diagnosis of multiple stroke (Fig. 1). Magnetic resonance angiography at onset showed bilateral occlusion of the posterior cerebral arteries, which reopened 1 month later (Fig. 2). Electrocardiogram showed no atrial fibrillation or other arrhythmias. Blood tests were almost normal except for an elevated D-dimer level of 9.7 μg/mL. Intensive systemic management was carried out and edaravone was administered, but her level of consciousness did not improve, so she was placed on central venous nutritional management. Consent for the presentation of the case was obtained from the patient's family.

There is a risk that COVID-19 infection might induce severe thrombosis due to hypercoagulable conditions, such as large vessel occlusive ischemic stroke.[3] According to the TOAST classification, this case was classified as a "stroke of unknown cause". Endothelial damage, hypercoagulability, viral myocarditis and hypoxic damage have been proposed as the pathogenesis of COVID-19-related stroke,[4] and in the present case, hypercoagulability was one of the causes of the stroke. In a multivariate analysis controlling for race/ethnicity, COVID-19 infection was significantly and independently associated with large vessel occlusive stroke, with an odds ratio of 2.4.[5] However, the relationship between omicron variant infection and cerebral infarction is unclear, as all of these reports of the relationship between cerebral

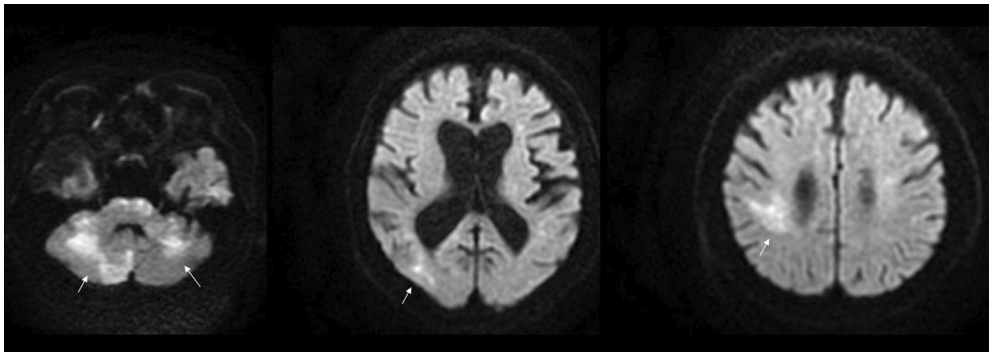

Figure 1 Diffusion-weighted image of the patient. High-intensity lesions were found in bilateral cerebellar hemispheres, right occipital lobe and parietal lobe, indicating the presence of multiple acute cerebral infarctions (shown by white arrows).