

A report of two cases of Werner's syndrome and review of the literature

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ABSTRACT

Two cases of Werner's syndrome are reported. The first case is that of a man with grey hair since his 20s, and alopecia since aged about 50 years. At the age of 53 years, Werner's syndrome was diagnosed, along with a malignant soft tissue tumour of the hand. The patient underwent ray amputation for the tumour. The subsequent histopathological diagnosis was synovial cell sarcoma, and the patient died of lung metastasis at 15 weeks postsurgery. The second case is that of a woman diagnosed with diabetes mellitus when aged 34 years. At 39 years, a bilateral cataract was diagnosed and at 40 years, diabetic gangrene of the left calcaneal region and calcaneal osteomyelitis necessitated left below-knee amputation. The incidence of Werner's syndrome in Japan is extremely high (about

1000 of the around 1300 cases reported worldwide) compared to other countries. Most patients develop malignant tumour or arteriosclerosis, the most important complications of this syndrome. The average life expectancy for patients with Werner's syndrome is 46 years. The incidence of epithelial cancer and mesenchymal sarcoma is 10 times that of the general population. The onset of symptoms of Werner's syndrome generally precedes any later symptoms of associated conditions, such as malignant tumour. Therefore, early recognition of Werner's syndrome is important to assist identification of malignant tumours at an early stage in this patient group.

Key words: arteriosclerosis; chondrosarcoma, mesenchymal; ossification, heterotopic; osteomyelitis; sarcoma, synovial; Werner syndrome

INTRODUCTION

Werner's syndrome is a hereditary systemic disease. Clinical characteristics including small stature, scleroderma-like skin alterations, juvenile cataracts, and premature facial ageing. This syndrome has been reported most frequently in the ophthalmologic and dermatologic literature, but has also been reported in the orthopaedic literature due to its complications of ectopic calcification, refractory ulcer, and joint contracture. We report 2 cases of Werner's syndrome—one associated with a malignant soft tissue tumour of the hand, and the other associated with a refractory calcaneal ulcer.

CASE REPORTS

Case 1

A male patient presented to the Department of Surgery, Tokyo Medical University when aged 54 years. His major complaints at this time were swelling, and pain in the left hand. The medical history taken identified that his parents were consanguineous, but that there were no symptoms of note in his 5 siblings and 2 children. The patient reported that he had been short in stature since childhood, and grey-haired since his 20s. He had noticed his voice weakening with a high pitch since about the age of 30 years, along with skin atrophy in the peripheries of the extremities. At the age of 37 years, the patient had an ulcer over his right ankle joint, which took 6 months to heal. When aged 40 years, he had surgery for a left eye cataract. When aged about 50 years he noted increasing alopecia. He also commenced treatment for angina at this time. At the age of 53 years, he visited a doctor in response to dull pain and a small growth in the left hypothenar region. Two months later, he was referred to our department due to abnormal findings of the 4th and 5th metacarpi on X-ray.

General physical examination on admission revealed that he was only 142.5 cm in height and 41.5 kg in weight. His extremities were thin. Atrophied skin, and decreased subcutaneous fat and muscle were observed in the periphery of the extremities. His external genitalia appeared atrophied. There was extensive abnormal pigmentation of the skin and telangiectasis evident. His hair was generally scarce and markedly grey. His face looked aged, and he had a beak-shaped nose. His voice was high-pitched and hoarse. Range of motion of the ankle joints was limited to -5° on dorsiflexion and 30° on plantar flexion, and mobility of the skin

was markedly reduced. The ulnar surface of the left hand was oedematous. A partially irregular, elastic, hard mass was felt on the surface between the 4th and 5th metacarpi, showing adhesion to the skin. Heat and tenderness were noted on examination but no fluctuation or pulsation was evident.

Laboratory findings included decreased glucose tolerance, decreased natural killer cell activity, and an increased T4/8 ratio. X-ray findings at presentation included irregular erosion of the cortex of the 4th and 5th metacarpi and the distal phalanx, and a tumour shadow in the soft tissue on the ulnar surface (Fig. 1). Angiography of the hand revealed arterial deviation, contraction, and calibre variation, but no tumour stain, blood pool, or arteriovenous shunt. Computed tomography (CT) scanning of the hand indicated a broad defect of the palmar cortex of the 4th and 5th metacarpi, and a soft tissue tumour shadow with an indistinct border.

In addition, calcification was identified in the



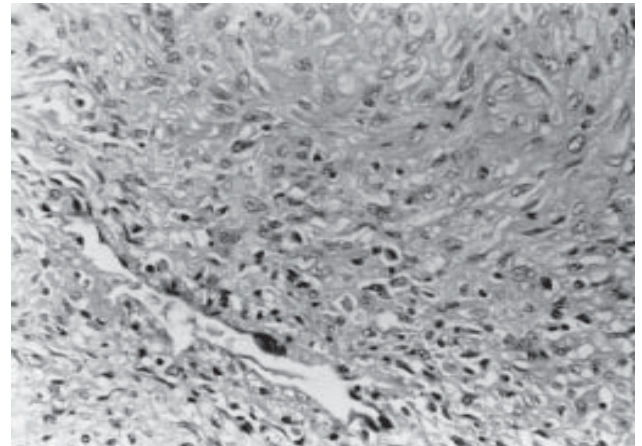
Figure 1 Case 1: X-ray of the hand showing erosion of the 4th and 5th metacarpi.



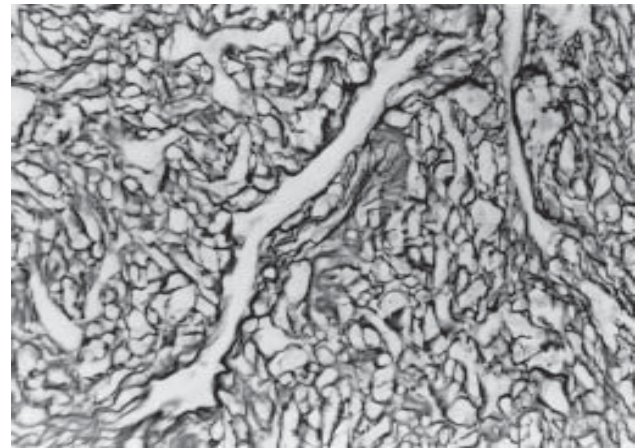
Figure 2 Case 1: X-ray of the knee showing calcification in the quadriceps tendon and the patellar ligament.

quadriceps tendon and patellar ligament (Fig. 2), as well as in the triceps tendon and the Achilles tendon. Based on the above findings, a diagnosis of Werner's syndrome associated with malignant soft tissue tumour in the hand was made.

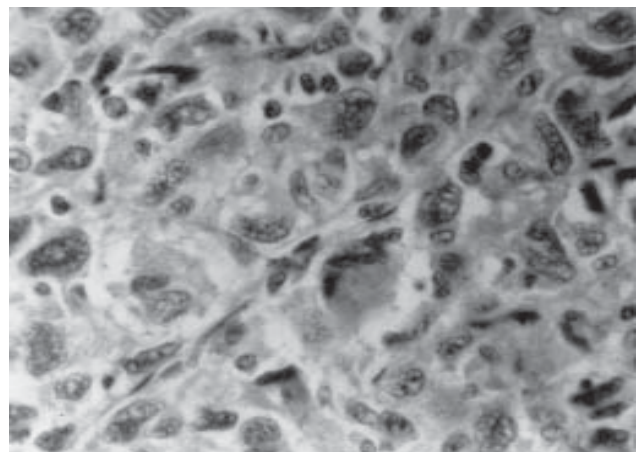
Ray amputation was undertaken of the 4th and 5th metacarpal below the carpometacarpal joint. The patient refused below-elbow amputation. The tumour consisted of a grey-white, solid soft tissue tumour lacking tunica and substituting part of the ring finger, the 5th finger flexor fascia, the extensor tendon, the 2nd and 3rd palmar interosseous muscles, the 3rd and 4th lumbricalis muscles, and the dorsal interosseous muscles. The palmar cortex of the diaphysis of the 4th and 5th metacarpal was fractured. Histopathological investigations of tumour tissue showed the cell matrix was hyalinized, and there was a cleft covered with atypical cells in the region of high cellularity. Many tumour cells were spindle-shaped polynuclear cells (Fig. 3a). Most cells resembled epithelial



(a)



(b)



(c)

Figure 3 Case 1: histological findings (a) the specimen shows a cleft covered with atypical cells, and the presence of many spindle-shaped tumour cells (H&E, x 100), (b) a silver-stained specimen shows the fibres and tumour cells forming a mesh (x 100), and (c) colloidal iron staining shows positive substances in the cells, suggesting the presence of mucopolysaccharides (x 400).

cells, partially enriched with cytoplasm, but not demonstrating typical epithelial-like structure. Fibres staining silver were thick and were surrounded by tumour cells to form a mesh (Fig. 3b). Staining with colloidal iron revealed positive substances in the cells, suggesting presence of mucopolysaccharides (Fig. 3c). Based on the above findings, a pathological diagnosis of monophasic spindle cell type synovial cell sarcoma was made. The patient died of pulmonary metastasis 15 weeks after surgery.

Case 2

A female patient presented to the Department of Surgery, Tokyo Medical University with refractory ulceration in the right calcaneal region when aged 56 years. The medical history taken identified that her parents were cousins but there were no abnormalities noted in her 3 siblings; and no other family members had Werner's syndrome.

At about 25 years of age, the patient had noticed dermal atrophy in the periphery of the extremities. She began treatment for diabetes mellitus at a local clinic when aged 34 years. At the age of 35 years, she became climacteric and thereafter, her hair became grey, and her voice tone changed. At 39 years, bilateral cataracts were diagnosed and she underwent surgery at the Department of Ophthalmology, Tokyo Medical University. In the same year at another hospital, below-knee amputation was performed on the left leg for diabetic gangrene in the left calcaneal region. At 55 years, topical treatment was commenced at the Department of Dermatology, Tokyo Medical

University, for a callosity in the right sole of the calcaneal region that had developed without an obvious precipitating cause. The lesion gradually expanded and became ulcerated in the centre, with noticeable discharge of pus, and the patient was referred to our department at this time.

Physical examination on admission revealed that the patient was only 148 cm in height and 32 kg in weight, with thin extremities, markedly atrophied skin and subcutaneous fat, and non-elastic, glossy skin in the periphery of the extremities. Grey hair and alopecia were observed, and her 'bird-like' face appeared older than her age. Her voice was hoarse with a rather high pitch. An ulceration 6 x 7 cm in size was observed at the protruding region of the right calcaneus, with the surrounding skin showing necrosis. The base of the ulceration was covered with poorly developed granulation tissue. The calcaneal cortex was partially exposed from the centre. Joint contracture was noted in the foot joint and the toes (Fig. 4).

Laboratory findings on admission were an increased erythrocyte sedimentation rate of 55 mm/h, and C-reactive protein of 0.7 mg/dL. Mild anaemia (haemoglobin, 95 g/L) and hyperglycaemia (blood glucose, 209 mg/dL) were evident. On plain X-ray, the calcaneus showed marked destructive osteoclasia at the centre of the calcaneal body, and pathologic fracture and osteolysis at the same site, involving the talocalcaneal joint with osteoclastic alteration (Fig. 5). Other X-ray examinations revealed bilateral ectopic calcification in the triceps tendon, the quadriceps tendon, the patellar ligament, and the ankle calcaneal



Figure 4 Case 2: Calcaneal ulceration with partial exposure of the calcaneus and the border and floor of the ulceration covered with poor granulation tissue.



Figure 5 Case 2: X-ray of the calcaneus before hyperbaric oxygen therapy, showing marked osteoclasia at the centre of the calcaneal body and at the surface of the talocalcaneal joint.

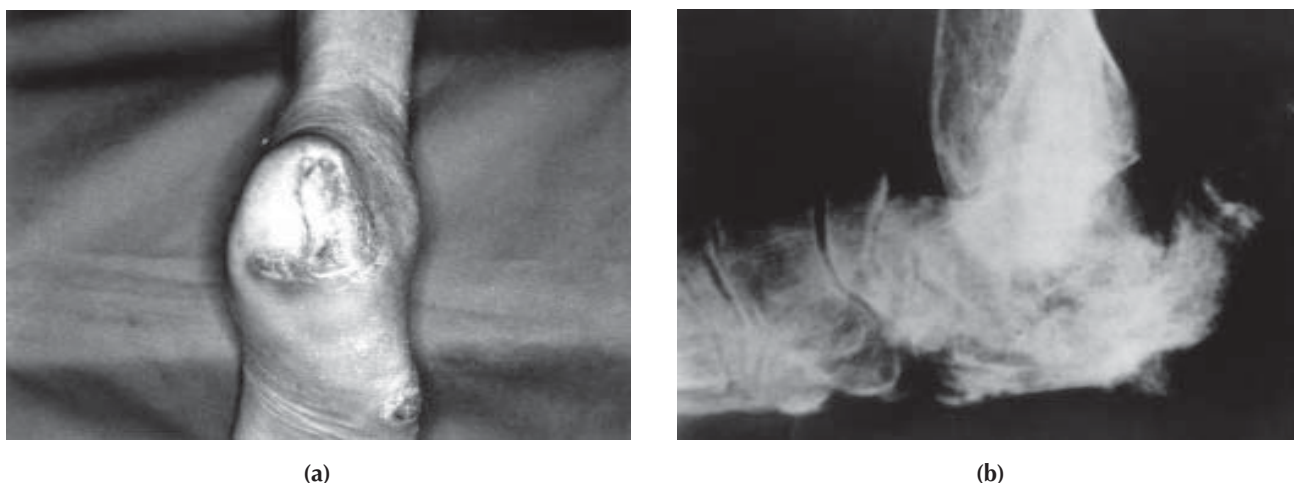


Figure 6 Case 2: findings following hyperbaric oxygen therapy (a) gross ulceration evident reduced (b) X-ray of the calcaneus showing induration in the pressurised destructive region of the calcaneus and repair of the bone.

region, and osteoporosis corresponding to Grade III of Singh's classification.¹ Histopathological examination of specimens from the ulcerated region showed that the bone marrow contained fibrous granulation tissue, infiltrated with lymphocytes, and plasmocytes, indicating chronic osteomyelitis. There was no evidence of malignancy.

Based on the above results, a diagnosis of Werner's syndrome associated with refractory calcaneal ulceration and calcaneal osteomyelitis was made. There was no improvement in the ulceration following curettage and repeated local treatments. Surgical therapy, such as skin grafting and amputation of the affected extremity were considered, but invasive treatments were abandoned because of the patient's poor general condition, and refusal for surgery. The decision was made to undertake hyperbaric oxygen therapy in order to improve local circulation. This was applied 99 times with a schedule of 2.0 atm for 80 minutes. Prior to hyperbaric oxygen therapy, the ulceration was 6 x 7 cm in size, with calcaneal bone marrow exposed, and the skin at the border of the ulceration cornified and oedematous but with no bleeding. Hypothermic regions corresponding to the ulceration were observed by thermography. After hyperbaric oxygen therapy, the ulceration had shrunk to 3 x 5 cm. X-ray images revealed sclerosis of pressurised destructive regions of the calcaneus and some repaired bone. Thus, hyperbaric oxygen therapy was judged to be clinically effective in this case (Fig. 6). The patient's clinical course has since remained largely unchanged, and there has been no further development of osteoclasia.

DISCUSSION

Werner's syndrome was initially described by Werner² in 1904, when he reported 4 cases of brothers and sisters with symptoms and signs including juvenile cataract, pachyderma-like alteration of the extremities, small stature, premature ageing of the face, juvenile grey hair, and genital hypoplasia. In 1934, Werner's syndrome was described by Oppenheimer and Kugel³ as an independent disease, with additional endocrine abnormalities, such as osteoporosis and hyperglycaemia. To the best of the authors' knowledge, about 1300 cases reported around the world from 1916 to 2002, including about 1000 Japanese patients. Japan is an area of extremely high incidence of Werner's syndrome. We were able to locate 411 Japanese cases in the literature from 1916 to 2002 i.e. since the publication by Ishida,⁴ by conducting search of MEDLINE and Japanese databases. Cases were most frequently reported in the fields of dermatology and ophthalmology but infrequently in the field of orthopaedics, with only 45 Japanese cases reported.

Werner's syndrome is regarded as a representative model disease of early senility in human beings. This syndrome rarely appears before puberty, but thereafter is evident in signs such as a 'bird-like' face or generalised signs of senility (grey hair, alopecia, cataracts, and skin atrophy with refractory skin ulceration). It is also evident in diseases generally caused by ageing, such as arteriosclerotic diseases (myocardial infarction, cerebral infarction), diabetes mellitus with hyperinsulinaemia, hyperlipaemia, hyperuricaemia, and osteoporosis from the age of 30

Table 1
Characteristic features of Werner's syndrome*

| Diagnostic criteria by Irwin and Ward ⁶ | Incidence of features reported (%) in Japanese cases (n=411) | Presence/absence in current cases | |
|---|--|-----------------------------------|----------|
| | | Case 1 | Case 2 |
| Characteristic habitus and stature | | | |
| Short stature (from adolescence) | 86.6 | Present | Present |
| Slender extremities with stocky trunk | 86.3 | Present | Present |
| Beak-shaped nose | 75.7 | Present | Present |
| Premature senility | | | |
| Premature grey hair | 86.1 | Present | Present |
| Premature baldness | 70.0 | Present | Present |
| Atrophic skin | 85.4 | Present | Present |
| Weak and high-pitched voice | 76.1 | Present | Present |
| Arteriosclerosis | 54.0 | No data | No data |
| Juvenile cataracts | 94.8 | Present | Present |
| Scleroderma-like changes | | | |
| Atrophic skin and subcutaneous tissues | 86.3 | Present | Present |
| Circumscribed hyperkeratosis | 70.5 | Present | Present |
| Ulcers over the malleoli of the ankles, Achilles tendon, heels and toes | 69.5 | Present | Present |
| Other manifestations | | | |
| Tendency to diabetes mellitus | 67.2 | Marginal | Marginal |
| Hypogonadism | 64.2 | Absent | Absent |
| Osteoporosis | 54.7 | Present | Present |
| Localised calcification | 57.4 | Present | Present |
| Tendency to occur in siblings | 48.7 | Absent | Absent |

* Data obtained by the authors' search of MEDLINE and Japanese databases in years from 1916 to 2002

years. In many cases the patient dies of malignant tumours or arteriosclerotic diseases, at an average age of 46 years.⁵ Irwin and Ward⁶ identified a total of 17 features associated with Werner's syndrome. Both cases reported here exhibited 13 of the possible 17 features described (Table 1).

The most problematic complications of Werner's syndrome are arteriosclerosis and malignant tumours. The frequency of malignant tumours reported ranges from 5.6% to 25%.⁷ In Japanese cases, this figure is 20.7% (85 of 411 reported cases). Of the 411 Japanese cases, 25 patients (6.1%) died of malignant tumours (Table 2); which is considerably higher than that of the Japanese general population (0.3%).⁷ Moreover, this is the most common cause of death in reported cases of Werner's syndrome in Japan. For the general population, epithelial cancer has an incidence rate 10 times that of mesenchymal sarcoma, but among patients with Werner's syndrome the incidence is approximately equal (Fig. 7). An increased incidence of thyroid cancer, malignant melanoma, and osteosarcoma and soft tissue sarcoma is evident. In our search of the literature, benign tumours were found in

Table 2
Causes of death in reported cases of Werner's syndrome*

| Cause of death | Number |
|--|-----------|
| Malignant tumour | 25 |
| Cardiac failure, myocardial infarction | 8 |
| Pneumonia | 3 |
| Respiratory failure | 3 |
| Disseminated intravascular coagulation | 2 |
| Hepatic failure | 2 |
| Renal failure | 2 |
| Cerebrovascular disorder | 2 |
| Total | 47 |

* Data obtained by the authors' search of MEDLINE and Japanese databases in years from 1916 to 2002

a total of 37 Japanese patients, including 18 patients with mesenchymal. However, there were no reports in the literature of synovial sarcoma as described in this report. Although synovial sarcoma was often reported in other sites, our case is the only one reported to occur in the hand (Fig. 8). All 85 reported cases

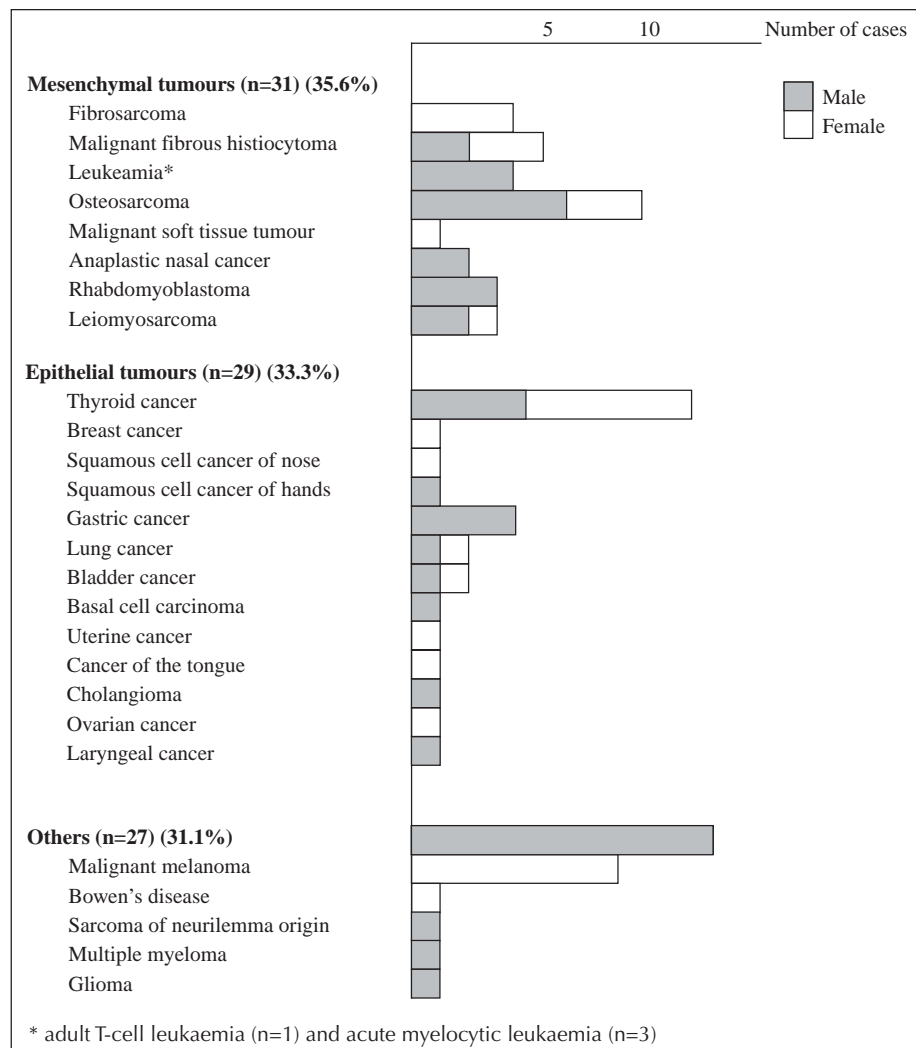


Figure 7 Types of complicated malignant tumours identified in 85 patients of Werner's syndrome according to the authors' search of MEDLINE and Japanese databases from 1916 to 2002.

with malignant tumour were investigated, and the age of onset of malignant tumour and Werner's syndrome clearly described. To the best of the authors' knowledge, the first manifestations of malignant tumour and Werner's syndrome among Japanese patients were at 41.4 and 24.7 years, respectively. Generally, the earlier manifestation of Werner's syndrome was more clearly demonstrated. As Hrabko et al.⁸ suggested, it is therefore important to recognise Werner's syndrome at an early stage to facilitate identification of subsequent malignant tumours.

Immunological abnormalities, such as a decrease in natural killer cell activities or a decrease in T-cell subpopulations, have been associated with malignant tumour development,⁹ as well as DNA ab-

normalities.¹⁰ It is presumed that cellular life span is decreased after telomeres are shortened due to DNA inherited abnormalities, and these phenomena promote chromosome instability, providing a platform for accelerated manifestation of malignant tumours in general.

With respect to refractory ulceration, 189 (46.0%) of the 411 reported Japanese cases had associated refractory ulceration, while 13 (3.2%) had osteomyelitis, with the most common site the extremities. A total of 156 (82.5%) of the 189 cases of refractory ulceration and 10 (76.9%) of the 13 cases with osteomyelitis affected the periphery of the lower extremities (Fig. 9). The causes of refractory ulceration may include disorders of the vasculature, such as arteriosclerotic

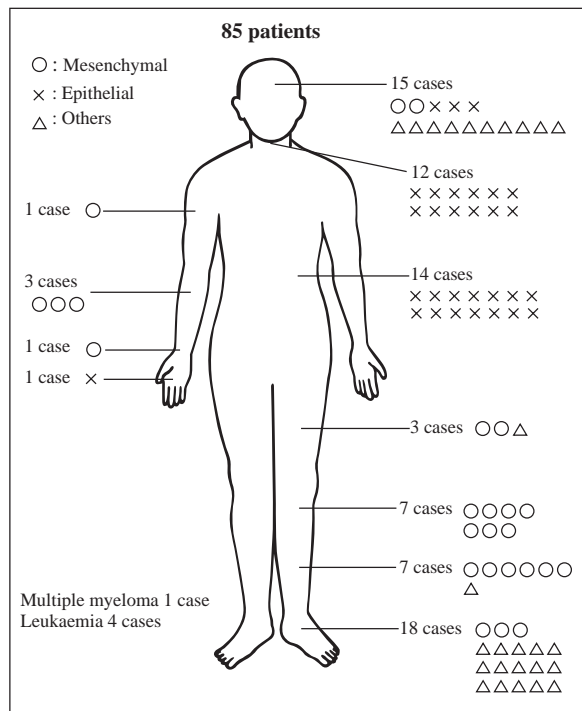


Figure 8 Sites of onset in 85 patients with complicated malignant tumour identified in the Japanese cases of Werner's syndrome according to the authors' search of MEDLINE and Japanese databases from 1916 to 2002.

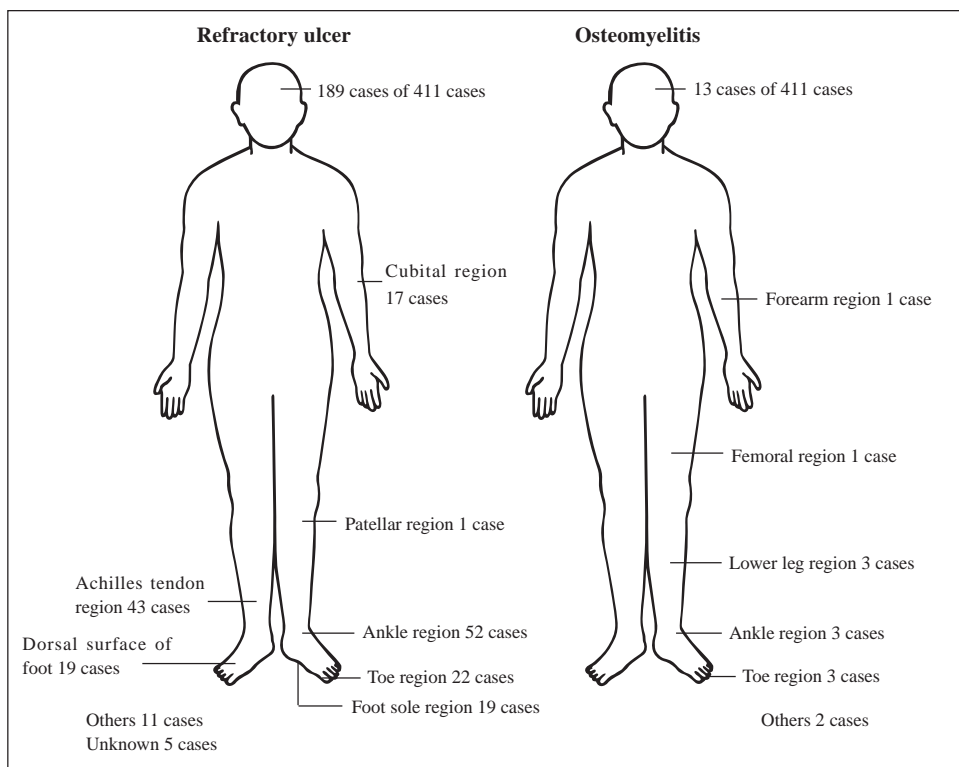


Figure 9 Common sites of refractory ulcer and osteomyelitis tumour identified in the Japanese cases of Werner's syndrome according to the authors' search of MEDLINE and Japanese databases from 1916 to 2002.

Table 3
Orthopaedic complications and sites in reported Japanese cases*

| Site | Number |
|--|--------|
| Ectopic calcification, 154 patients (37.5%) | |
| Achilles tendon | 71 |
| Triceps tendon | 15 |
| Quadriceps tendon | 6 |
| Heel, foot sole | 7 |
| Patellar ligament | 7 |
| Finger | 6 |
| Ankle | 6 |
| Toe | 4 |
| Others | 17 |
| Unknown | 15 |
| Articular contracture, deformity, 99 patients (24.0%) | |
| Toe | 24 |
| Ankle joint | 21 |
| Hallux valgus | 19 |
| Finger | 15 |
| Knee joint | 6 |
| Wrist joint | 5 |
| Elbow joint | 1 |
| Others | 8 |

* Data obtained by the authors' search of MEDLINE and Japanese databases from 1916 to 2002

changes in the blood vessels and decreases in local blood flow, extrinsic stimulation of the atrophic skin that has decreased ability to support the tissue, and complications of generalised metabolic disorders such as diabetes mellitus. 59 (31.2%) of 189 Japanese patients with ulcer received only conservative treatment, and 57 patients of those refractory to conservative treatment received combined surgical treatment. Surgical treatment, other than amputation of a lower limb, was performed in 37 patients but the results were poor for 16 (43.2%) patients. 37 (19.6%) subsequently underwent amputation of a lower limb.

The mechanism of action of hyperbaric oxygen therapy for ulceration involves resolution of local hypoxia due to physically elevated solubility of oxygen and promotion of the formation of fresh granulation tissue.¹¹ We consider hyperbaric oxygen therapy useful, based on our experience. However we could not find any other reports of hyperbaric oxygen therapy applied to refractory ulceration associated with Werner's syndrome in the literature between 1916 and 2002. Other representative orthopaedic complications include ectopic calcification and joint contracture, which tend to occur in the periphery of the extremities. Calcification of

the Achilles tendon and contracture/deformity of the toes, including hallux valgus, is common (Table 3).

In terms of pathogenesis, several theories have been proposed including embryological defects in the germ layer becoming evident at puberty,¹² polyglandular dysfunction of endocrine functions (e.g. parathyroid dysfunction and pituitary dysfunction), and abnormal metabolism in connective tissue. Pathological and biochemical studies point to abnormal metabolism in connective tissue as the most likely explanatory theory because abnormal mucopolysaccharides and fibroblasts are found in patients with Werner's syndrome.^{13,14} The genes associated with Werner's syndrome were isolated and identified using the positional cloning method in 1996.¹⁵

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