

## Werner's syndrome: a quite rare disease for differential diagnosis of scleroderma

Cemal Bes · Şeref Vardı · Melih Güven ·  
Mehmet Soy

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**Abstract** Werner's syndrome (WS) is an autosomal recessive disorder characterized by premature aging. The main features of the disease are scleroderma-like skin appearance, premature atherosclerosis, short stature, diabetes mellitus, early osteoporosis and early aging. Herein, we describe a patient with WS, who has scleroderma-like skin changes and discuss the literature about WS as a disease in the differential diagnosis of systemic sclerosis.

**Keywords** Werner syndrome · Scleroderma · Digital ulcers

### Introduction

Werner's syndrome (WS) is an autosomal recessive disease associated with premature aging. Both genders are affected equally. The estimated incidence is one case in one million individuals [1]. WS was first described in 1904 by Otto Werner [2]. A gene called "Werner's Syndrome Gene (WRN)" is considered to be responsible for the mutations that play a critical role in the pathogenesis of the syndrome [3]. The manifestations are widespread, and many organs may prematurely change usually associated with aging. Generally, the first clinical sign is a lack of the pubertal growth spurt during the teen years and early aging [4].

Dermatologic manifestations are including scleroderma-like appearance of the skin, lower extremity ulcers or calluses, thinning and greying of hair or baldness, nail dystrophy or loss, wrinkling and aging of the face and skin cancers. Clinical findings of skin and progression of the disease are similar to that of systemic sclerosis. Herein, we report a patient with WS who has scleroderma-like skin changes and discuss the literature about WS as a disease in the differential diagnosis of systemic sclerosis.

### Case

A 40-year-old man was admitted to the department of orthopedics. He has been suffering from ischemic changes at the lower extremity for 2 months and he underwent right below-knee amputation due to necrosis 1 week ago. He also had amputations of left below-knee 5 years ago and distal phalanges of left fingers 1 year ago linked with necrosis. Initially, a diagnosis of scleroderma was taken by an internist. He was referred to rheumatology unit for investigation of etiology of skin changes and gangrene of the leg.

Since childhood, he had short stature, thin and wrinkle skin, and premature grayed hair. Bilaterally cataract operation was performed 12 years ago and was diagnosed as diabetes mellitus in the same year. His parents were not intermarried. He has two healthy daughters aged 9 and 13 years. Bilaterally knee amputations had performed to her sister due to peripheral arterial occlusions.

On physical examination, "bird-like face", high-pitched voice, tight and shiny face skin, beaked nose and perioral radial scratching that remind scleroderma-like changes were noted (Fig. 1). Because of bilateral below-knee amputation, he was 146 cm tall and weighed 31 kg. Thin

C. Bes (✉) · Ş. Vardı · M. Soy  
Internal Medicine, Rheumatology Department, Izzet Baysal  
Medical Faculty, Abant Izzet Baysal University,  
Gölköy, Bolu, Turkey  
e-mail: cemalbes@hotmail.com

M. Güven  
Orthopedics Department, Izzet Baysal Medical Faculty,  
Abant Izzet Baysal University, Gölköy, Bolu, Turkey

**Fig. 1** “Bird-like face” appearance of the patient



**Fig. 2** Atrophic skin changes of both hands and necrotised plaques on the left hand

and atrophic skin, apparent vessels on the dorsum of his hands, necrotized plaque on the amputated sites of left distal-fingers were detected (Fig. 2). Laboratory findings were an increased erythrocyte sedimentation rate of 98 mm/h, glucose level of 18 mmol/l, urea level of 41 mg/dl, creatinine level of 0.95 mg/dl, cholesterol level of 230 mg/dl and triglyceride level of 385 mg/dl. In the echocardiography, ejection fraction was 55%,  $\frac{1}{2}$  apex of septum was hypo kinetic and aortic valve was sclerotic that were consistent with coronary artery disease.

Radiography of both hands showed osteosclerosis of the fingers and extensive calcification in arterioles (Fig. 3). T-score of left femur was  $-4.2$  in dual energy X-ray absorptiometry.

Presence of typical clinical characteristics, included premature aging, family history, and other clinical features, which are defined at above, lead us to make a diagnosis of WS. The clinical diagnostic criteria of WS and findings of our patient were outlined at Table 1 [5]. Genetic analysis was not performed due to technical reasons.



**Fig. 3** Osteosclerosis of the fingers and extensive calcification in arterioles

Hypoglycemic agents, acetylsalicylate, statine, calcium channel blocker, calcium + vitamin D and biphosphanate therapy were started.

## Discussion

Werner's syndrome was first described in 1904 by an ophthalmologist named Otto Werner [2]. Thirty years later, Oppenheimer and Kugel [6] added osteoporosis and hyperglycemia to the syndrome. Although the incidence is 1/1 million, the syndrome is extremely high in Japan (about 1,000 of the around 1,300 cases that reported between 1916 and 2002 were Japanese) [7]. Males and females are equally affected [1]. It is a progeroid syndrome caused by mutations at the WRN helicase locus. Some features of this disorder are also present in laminopathies caused by mutant LMNA encoding nuclear lamin A/C [8]. Premature greying

**Table 1** Clinical diagnostic criteria of Werner syndrome and positive findings of presented

| Major signs and symptoms (onset over 10 years old)                                                                                                                                                  | In our patient presenting with ischemic disease |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| Cataracts (bilateral)                                                                                                                                                                               | Present                                         |
| Characteristic dermatological pathology (tight skin, atrophic skin, pigmentary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy) and characteristic facies ('bird-like' face) | Present                                         |
| Short stature                                                                                                                                                                                       | Present                                         |
| Premature greying and/or thinning of scalp hair [Parental consanguinity (third cousin or closer) or affected sibling]                                                                               | Present                                         |
| (Positive 24-h urinary hyaluronic acid test when available)                                                                                                                                         |                                                 |
| Additional signs and symptoms                                                                                                                                                                       | Present                                         |
| Type 2 diabetes mellitus                                                                                                                                                                            | Present                                         |
| Hypogonadism (secondary sexual underdevelopment, diminished fertility, testicular or ovarian atrophy)                                                                                               | Present                                         |
| Osteoporosis                                                                                                                                                                                        | Present                                         |
| Osteosclerosis of distal phalanges of fingers and/or toes (X-ray diagnosis)                                                                                                                         | Present                                         |
| Soft tissue calcification                                                                                                                                                                           | Present                                         |
| Evidence of premature atherosclerosis (e.g., history of myocardial infarction)                                                                                                                      | Present                                         |
| Neoplasms: mesenchymal (i.e., sarcomas), rare (unusual), or multiple                                                                                                                                | Absent                                          |
| Abnormal voice (high-pitched, squeaky, or hoarse)                                                                                                                                                   | Present                                         |
| Flat feet                                                                                                                                                                                           | Absent                                          |
| Definite diagnosis                                                                                                                                                                                  |                                                 |
| All the major signs and two additional signs                                                                                                                                                        | Fulfilled for our patient                       |
| Probable diagnosis                                                                                                                                                                                  |                                                 |
| The first three major signs and any two others                                                                                                                                                      |                                                 |
| Possible diagnosis                                                                                                                                                                                  |                                                 |
| Either cataracts or dermatological alterations and any four others                                                                                                                                  |                                                 |
| Exclusion of diagnosis                                                                                                                                                                              |                                                 |
| Onset of signs and symptoms before adolescence (except short stature)                                                                                                                               |                                                 |

or loss of hair, voice alterations, and sclerotic changes of skin, bilateral cataract, type 2 diabetes mellitus, hypogonadism, osteoporosis, atherosclerosis, and predisposition for neoplasm occurs following. Scleroderma-like changes of the face results with characteristic "bird-like face" appearance in third or fourth decade [3]. Also perioral radial scratching, thinning of hair, alopecia, wrinkling of skin, lose of subcutaneous fat tissue, soft tissue calcifications, nail dystrophies, flat feet, hyperkeratosis, and leg ulcers are the typical findings of the syndrome [2, 3]. Many of those dermatologic sign and symptoms resemble the characteristics of systemic sclerosis.

The main complications of WS are high incidence of premature atherosclerosis and malign neoplasm. The incidence of malign neoplasm is between 5.6 and 25% [9]. Especially, thyroid cancers, malign melanomas, osteosarcomas, meningiomas, soft tissue sarcomas, and hematological malignancies had been reported in a high frequency [10]. Atherosclerosis may exhibits unique characteristic in WS and 50% of mortality in these patients are associated

with myocardial infarction, cardiac failure, and cerebral infarct due to atherosclerosis [7, 11]. Atherosclerosis also results refractory lower extremity ulcers. Skin ulcers cause seriously morbidity in a half of patients [12, 13]. These ulcers resemble that of seen at systemic sclerosis.

Severe and premature atherosclerosis was found in our patient. Extremity ulcers and necrosis were developed because of atherosclerotic peripheral artery disease that necessitated extremity amputations. Extensive calcification in vessels had showed the severity of atherosclerosis on direct X-ray. On echocardiographic evaluation, hypokinesia of myocardium (consistent of coronary artery disease) was detected. On the other hand, premature atherosclerosis is not features of systemic sclerosis [14].

Systemic sclerosis (scleroderma) is a connective tissue disease characterized by fibrosing of visceral organs and skin [15]. Recurrent digital ulcers due to vascular involvement result in pain, dysfunction and additionally lose of tissue, and extremity [16]. Recurrent digital ulcers, necrosis of extremities, tight-atrophic skin, and perioral

scratching are the common features of both WS and systemic sclerosis as mentioned above. Absences of progeria, premature cataract, tendency to atherosclerosis, and early development of diabetes mellitus and presences of Raynaud phenomena, auto antibodies may helpful for distinguishing systemic sclerosis from WS.

In conclusion, WS should be considered in patients who have scleroderma-like skin lesions, digital ulcers, and extensive atherosclerotic peripheral artery disease. Accurate history and rheumatologic tests will contribute to differential diagnosis between two diseases.

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