Werner's Syndrome Presenting Without Hypogonadism: Differential Diagnosis

HİPOGONADİZM OLMADAN SEYREDEN WERNER SENDROMU

Oya TOPALOĞLU, MD,[a] Bekir ÇAKIR, MD,[a] Cevdet AYDIN, MD,[a]
Tuba AĞAÇ, MD,[a] Ayla ÖZKABA, MD,[a]

[a]Department of Endocrinology and Metabolism Diseases, Atatürk Education and Research Hospital, ANKARA

Werner's syndrome is a rare, autosomal recessive condition and is characterized by premature aging in the adult, scleroderma-like skin changes involving especially the extremities, cataract, muscular atrophy, tendency to Diabetes mellitus, aged appearance of the face, baldness, and high incidence of neoplasm. Several endocrinological abnormalities including hypogonadism and impaired glucose tolerance were reported in such patients.[1] Here we described a 45 -year-old man with Werner's syndrome associated with left ankle osteomyelitis, extensive tendinopathy of the ankles, osteoporosis of the extremities, diabetic foot infection, typical physical appearance and without hypogonadism.

The 45 year-old male patient had an 18-year history of diabetes mellitus and he had used several oral antidiabetic drugs irregularly during this period. He was hospitalized in our clinic because of a diabetic foot infection on the lateral malleolus of the left foot. He has been married for 25 years and had 4 children. He gave a history of bilateral cataract operation 16 years ago and he has been wearing eyeglasses since then. Although he described a serebrovascular attack and consequential right hemiparesis 3 years ago, he did not have any sequela at presentation.

On physical examination, the height was 159 cm and the body weight was 43 kg. His mental status was well. His face had a bird-like appearance with micrognathia and a beaked nose; in addition, he had an older facial appearance compared to his age (Figure 1). His hair and beard were sparse and he declared that his hair has been grayish for the last 15 years. The skin and the subcutaneous tissues were atrophic and the skin overlying the feet and hands was tight and sclerotic (Figure 2). The skin of the lower extremities under the patella was indurated and scaled. He had a 2 x 2 cm infected ulcer on the lateral malleolus of the left foot (Figure 3). Bilateral ankle joints were extremely stiff and joint motility was limited. There was no sign of joint swelling or pain.

Laboratory examination revealed a high level of fasting and postprandial plasma glucose. Excluding this finding, the blood biochemistry, urinalysis and complete blood count were all within normal ranges. Anti-nuclear antibodies, anti-double-stranded DNA, extractable nuclear antibodies including Scl-70 were all negative.

Ultrasonographic examination of the scrotal region was normal. Bone mineral densitometry revealed that the femur and lumber region were osteopenic. However, the left calcaneus region was osteoporotic.

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Yazışma Adresi/*Correspondence:* Oya TOPALOĞLU, MD
Atatürk Education and Research Hospital,
Endocrinology and Metabolism Diseases Department,
Bilkent, ANKARA
sudos@e-kolay.net

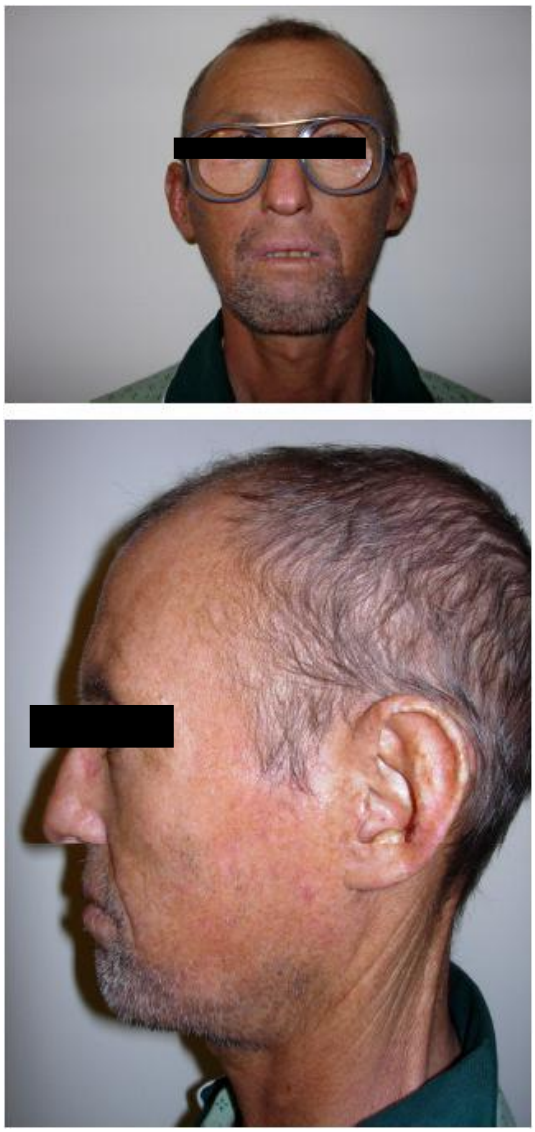

Figure 1. Facial appearance of the patient.

The patient was consulted to a dermatologist due to his skin lesions. A skin punch biopsy ob

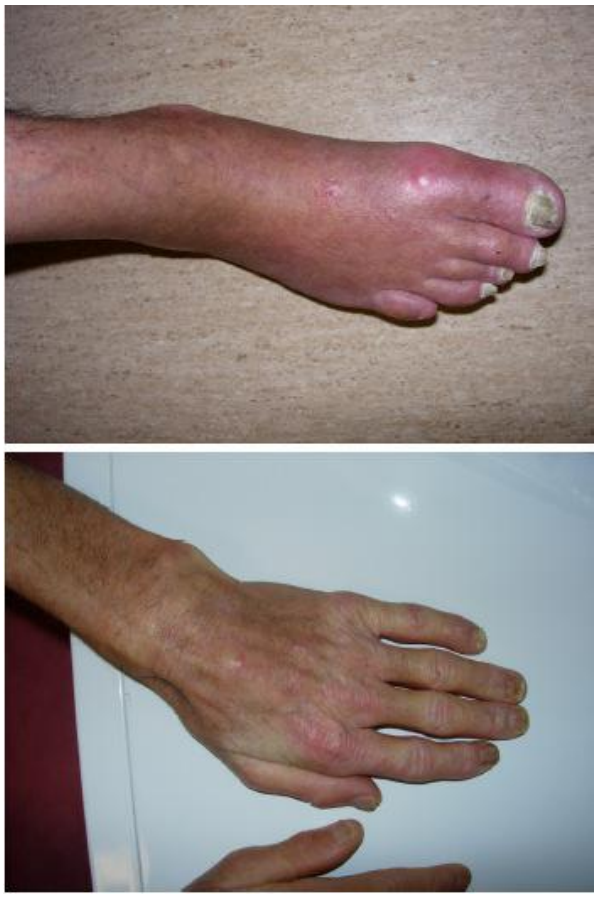

Figure 2. Atrophic, tight and sclerotic skin of the extremities.

The baseline values of all hormones were normal except LH; the baseline level of LH was at the upper limit of the normal values (Table 1). Our patient did not have hypogonadism. The dynamic tests of the hypotalamo-pituitary-adrenal axis were also performed. Although the adrenal reserve was normal, L-dopa and insulin induced hypoglycemia was not associated with growth hormone response of the pituitary gland (Table 2-4).

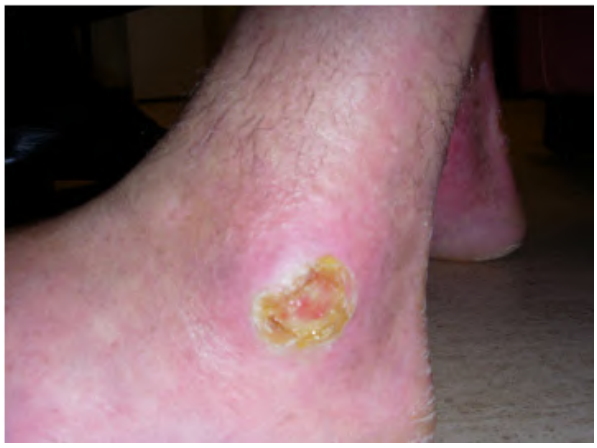

Figure 3. Infected ulcer on the lateral malleolus of the left foot.

Table 1. Baseline hormone profile of the patient.

Hormone values	Patient's value	Normal range
TSH (uIU/mL)	1.71	0.4-4
Free T3 (pg/mL)	3.34	1.57-4.71
Free T4 (ng/dL)	0.9	0.85-1.78
Plasma cortisol (ug/dL)	25	5-25
FSH (mIU/mL)	7.24	0.7-11.1
LH (mIU/mL)	8.16	0.8-8
Prolactin (ng/mL)	10.8	2.5-17
Total testosterone (ng/dL)	311	262-1593
Free testosterone (pg/mL)	10.2	8.5-40
Growth hormone (ng/mL)	0.6	0.06-5
Parathyroid hormone (pg/mL)	28.7	11-67

Table 2. Results of ACTH stimulation test.

Time	Plasma cortisol (ug/dL)
Baseline level	13
30 minutes	28
60 minutes	42.2
4 hours	>50
6 hours	>50

Table 3. Results of insulin-induced hypoglycemia test.

Time	Plasma Glucose (mg/dL)	Cortisol (ug/dL)	Growth Hormone (ng/mL)
0′	85	17.1	0.4
15′	79	12	0.4
30′	57	14.7	0.3
45′	40	15.9	0.3
60′	61	24	0.3
90′	73	16	0.2
120′	102	12	0.3

Table 4. Results of L-dopa stimulation test.

Time	Growth hormone (ng/mL)
0′	0.16
20′	0.14
40′	0.42
60′	2.1
90′	8.4

tained from the lower extremity skin revaled atrophic epidermis, subcutaneous tissue and morphea, which is a type of localized scleroderma. Magnetic resonance imaging of the left ankle, where the diabetic foot lesion was present, showed that subcortical benign cysts were present on the medial condyle of the tibia. In addition, a region of heterogenous appearance, 3 cm in diameter was present on the distal part of the fibula. This region was evaluated as osteomyelitis (Figure 4).

Mutation analysis of the patient was also performed.

On the basis of physical appearance, laboratory, skin, joint and bone findings, the patient was diagnosed with Werner's syndrome. It was interesting to find out that he had no hypogonadism.

The patient gave an informed consent for the publication of this case report.

Werner's syndrome is a rare autosomal recessive disorder first described by doctor Otto Werner in 1904.[2] It is characterized with scleroderma-like skin, premature ageing, leg ulcers and various endocrine abnormalities.[3]

Patients with Werner's syndrome have a typical physical appearance. They usually have a short stature with a stocky trunk and relatively thin extremities (Cushingoid appearance).[1] Our patient had these physical properties.

In the original paper by Otto Werner, the skin lesions were described as "scleroderma-like".[4] Goto et al reported that scleroderma-like skin changes were present in 96% of 196 Japanese cases.[1] Atrophy of skin, subcutaneous tissues and muscles, relatively stretched and thin lips, beaked nose, relatively recessive chin, hyperkeratosis on the soles of the feet, skin ulcers were the scleroderma-like skin changes observed in our patient.

Premature aging is one of the typical features of Werner's syndrome. Our patient had grayish hair and beard and lokalized osteoporosis. We

learned that his hair had become gray in his early twenties. Besides, he gave a history of cataract operation 16 years ago. Cataracts are frequently observed in patients with Werner's syndrome and they are generally posterior cortical or subcapsular type.[1] Early atherosclerosis also may occur in such patients. The leading causes of death for individuals with Werner's syndrome are myocardial infarction, malignancy and stroke. In our patient, we did not observe any signs of atherosclerosis or malignancy. However, the patient gave a history of cerebrovascular attack and subsequent hemiparesis 3 years ago; he had no sequela at presentation.

In addition to diabetic lesions, patients with Werner's syndrome have other orthopedic problems. For example, joint stiffness may occur in such patients. Our patient had bilateral ankle stiffness in addition to osteomyelitis of the distal region of the left fibula.

Several endocrinological abnormalities including hypogonadism and impaired glucose tolerance werereported in such patients.[1] We performed insulin-hypoglycemia and L-Dopa stimulation tests in our patient in order to evaluate the growth hormone response. Both tests were unresponsive. Our patient had 4 children. In Japanese cases, male hypogonadism was reported in 49% (60% hypergonadotropic, 9% hypogonadotropic and 9% unknown type) of patients with Werner's syndrome.[1] Abnormalities of thyroid function were reported in 14% of patients.[1] We did not observe any functional thyroid disorder in our patient.

Werner's syndrome may be classified in the group of chromosome instability syndromes. Mutation analysis was also performed in our patient. Conversion of the CAG codon encoding glycine to TAG stop codon at exon 30 was reported in a Turkish patient.[5] In our patient, after the sequence procedure, sequence encoding the CAG glycine was detected and no mutation was present at exon 30. WRN gene is a big gene so the analysis of the other exons couldn't be performed.

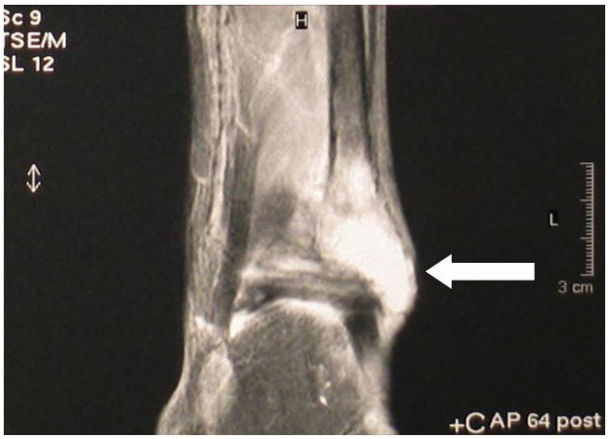

Figure 4. Osteomyelitic region, magnetic resonance imaging of the distal part of the fibula.

Effective treatment for Werner's syndrome is not present. Early recognition of Werner's syndrome is important to assist identification of malignant tumors at an early stage. Genetic counseling must be advised for the prevention of the disease. Although diabetes mellitus in Werner's syndrome may be insulin resistant, proper diet and oral antidiabetic agents are usually sufficient for the maintenance of euglycemia.[1] During the hospitalization period, our patient's blood glucose levels were regular despite very low insulin levels; only 20 units of insulin per day was sufficient.

In conclusion, Werner's syndrome is a rare autosomal recessive disorder characterized by premature aging, hypogonadism, diabetes mellitus, scleroderma-like skin lesions and typical facial appearance. Diagnosis is possible only in case of being aware of the disease. Early recognition is important for genetic counseling and for the identification of malignant tumors, atherosclerosis, diabetes, or osteoporosis at an early stage in this patient group since they are the most important factors for morbidity and mortality.

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