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Clinical Case

Beyond the Mask: Werner Syndrome Imitating Systemic Sclerosis

Tamer Acat, Yalkın Çalık, Nilay Erdik, Emre Bilgin, Emel Gönüllü

Sakarya University, Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Sakarya, Turkiye

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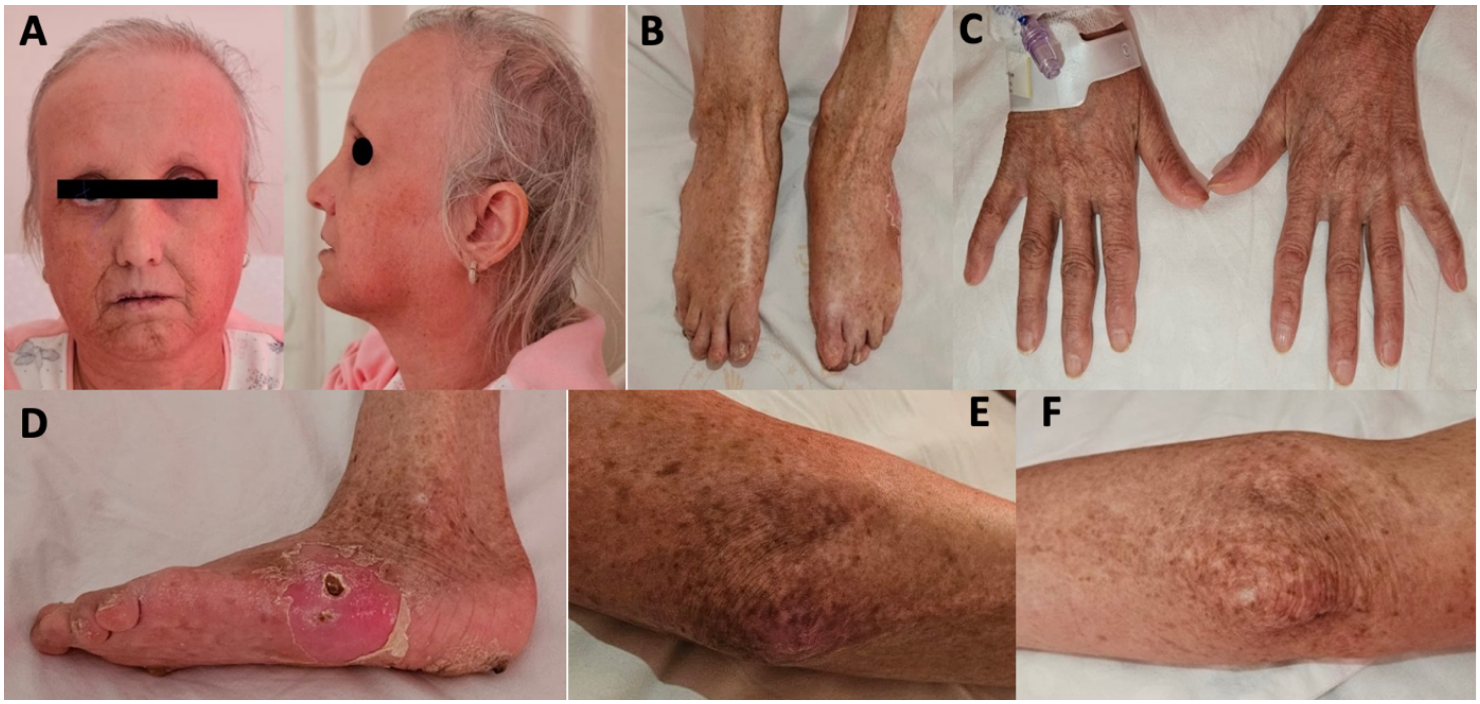

Figure 1. The appearance of the patient **a**, Gray hair, bird-like face appearance and alopecia; **b**, bilateral cutaneous webbing of 2-3 toes, skin tightness and thickening; **c,e,f**, skin depigmentation, right elbow ulcer, and scleroderma-like skin changes; **d**, Flat feet with hyperkeratosis and ulcer, skin depigmentation

I. INTRODUCTION

Werner syndrome (WS) typically remains asymptomatic until adolescence, presenting in the third decade with signs such as cataracts, skin atrophy, loss of subcutaneous fat, and graying and loss of hair, giving patients an aged appearance. Clinical findings include a high-pitched and hoarse voice, characteristic bird-like face, short stature with a stocky trunk, thin extremities, a cushingoid appearance, and flat feet. It is an autosomal recessive disease characterized by premature aging and various endocrine disorders such as diabetes mellitus, osteoporosis, and hypogonadism.

In rheumatology practice, scleroderma-like disorders represent a broad heterogeneous group characterized by sclerosis of the skin and underlying soft tissues, often influenced by genetic predisposition [1,2]. This group of diseases can have a different clinical course, ranging from

a benign disease with skin involvement to a widespread, systemic, life-threatening disease. Therefore, correct diagnosis is crucial regarding the disease's clinical course, treatment, and outcomes [3].

In this case, we emphasize the importance of a broader differential diagnosis in patients initially diagnosed and treated with systemic sclerosis (SSc), leading to the identification of WS.

II. CASE STUDY

A 49-year-old female presented with a 12-year history of skin thickening and tightening. She had previously been diagnosed with limited SSc based on skin biopsies and evaluations following complaints of Raynaud's phenomenon.

Upon physical examination, the patient lacked systemic sclerosis's typical skin and facial features. Laboratory tests revealed negative antinuclear antibodies (ANA), prompting a more detailed anamnesis:

- Her parents were cousins.
- The patient reported cataract surgery in both eyes at age 34.
- Signs of premature aging, including graying and balding, were noted to have begun in her early 30s (Figure 1).
- Early menopause and osteoporosis were diagnosed at age 35.
- Physical examination revealed ulcers in different areas, such as the elbows and feet, flat feet, and hyperkeratotic lesions on the soles of the feet (Figure 1).
- There was widespread skin tightening on the body, pigmentation on the hands, feet, and elbows, and an appearance resembling a bird's face (Figure 1).
- A hoarse and high-pitched voice was reported to have developed four years prior. She weighed 45 kg and was 155 cm tall.

Laboratory findings revealed negative autoantibodies (ANA, ENA panel, rheumatoid factor), normal complement levels (C3, C4), normal thyroid function tests, and normal tumor markers (CEA, CA 15-3, CA 19-9, and CA-125). Imaging studies showed no signs of malignancy. Luteinizing hormone and follicle-stimulating hormone levels were high, consistent with menopause, and this was evaluated as a finding of hypogonadism. Radiological findings included calcifications in both elbows and the left Achilles tendon and osteosclerosis of the distal phalanges of the feet (Figure 2). Bone density measurement revealed a lumbar T-score of -2.9, consistent with osteoporosis.

III. DISCUSSION

This case highlights the necessity of thorough clinical evaluation and a broad differential diagnosis in patients with atypical systemic sclerosis presentations, ultimately leading to the recognition of WS.

Werner Syndrome is a rare disease, with approximately 1,100 cases reported worldwide between 1904 and 1994; 75% of patients are of Japanese descent, and 70% are born to consanguineous parents [4]. The progression of WS can be summarized in three overlapping phases: early absence of pubertal growth and onset of aging

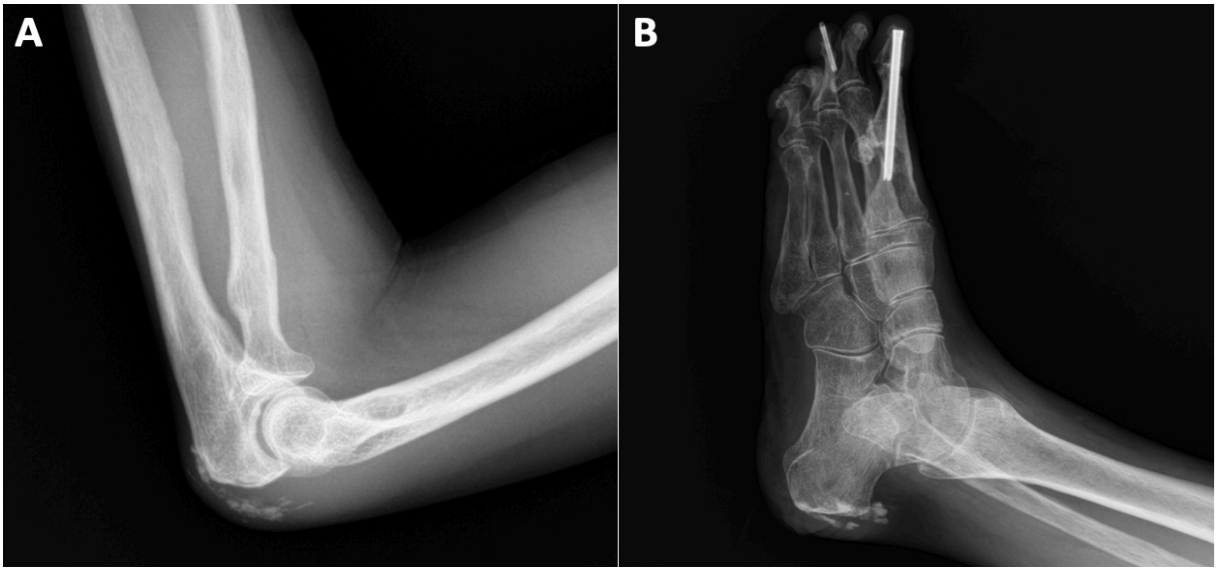

Figure 2. Radiologic imaging **a**, soft tissue calcification on right elbow; **b**, Achilles enthesitis and osteosclerosis of the distal phalanges

signs, reproductive issues and skin complications in the third decade, and finally, early onset of age-related diseases such as diabetes, atherosclerosis, and cancer [5].

The patient's 12-year history of skin thickening and complaints of Raynaud's phenomenon led to an initial diagnosis of limited SSc, reflecting the potential overlap in clinical presentations between these two conditions. However, the absence of typical SSc skin and facial features and a negative antinuclear antibody result prompted a more detailed anamnesis. The subsequent detailed history revealed key WS clues: parental consanguinity, early bilateral cataracts, premature aging signs (graying/balding), early menopause, and osteoporosis. Physical exam showed findings more typical of WS than SSc: recurrent ulcers (elbows/feet), pes planus, hyperkeratotic soles, widespread skin tightening with pigmentation (extremities/elbows), bird-like face, and a hoarse, high-pitched voice.As noted in other case series and reports [6, 7], patients with WS can be followed for years under a misdiagnosis of SSc due to overlapping clinical features. However, as demonstrated in our case, the absence of ANA and typical SSc skin findings should raise clinical suspicion for alternative diagnoses, including progeroid syndromes like WS.

The genetic basis of WS, involving mutations in the WRN locus on chromosome 8, leads to dysfunction of the Werner protein, a RecQ helicase with critical roles in DNA replication, repair, recombination, and transcription. The disruption of these processes underlies the premature aging and systemic manifestations observed in WS patients.

WS is caused by mutations at the WRN locus on chromosome 8. The WRN gene encodes a protein belonging to the RecQ helicase family, which exhibits ATPase, helicase, exonuclease, and single-stranded DNA annealing activities. This RecQ helicase enzyme plays a crucial role in DNA replication, repair, recombination, and transcription. The disruption of these processes underlies the premature aging and systemic manifestations observed in WS patients. Over 50 WRN disease mutations have been reported thus far [8]. Misdiagnosis risks unnecessary treatment and delayed management of WS complications. Thorough evaluation and detailed history are crucial for signs of premature aging; genetic testing should be used in cases of suspicion.

IV. CONCLUSION

In the differential diagnosis of systemic sclerosis, WS should be considered in ANA-negative patients lacking typical scleroderma skin findings. Accurate diagnosis is important for appropriate management, avoiding unnecessary treatments, and anticipating potential WS-related complications. This case highlights the importance of maintaining a broad differential diagnosis in rheumatology. It also highlights the value of sensitive clinical assessment in recognizing rare conditions that may appear to be common.

Table 1. The International Registry of Werner Syndrome

Cardinal signs and symptoms (onset over 10 years old) 1. Cataracts (bilateral) 2. Characteristic dermatological pathology (tight skin, atrophic skin, pigmentary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy) and characteristic facies (‘bird’ facies) 3. Short stature 4. Parental consanguinity (3rd cousin or greater) or affected sibling 5. Premature greying and/or thinning of scalp hair
Further signs and symptoms 1. Diabetes mellitus 2. Hypogonadism (secondary sexual underdevelopment, diminished fertility, testicular or ovarian atrophy) 3. Osteoporosis 4, Osteosclerosis of distal phalanges of fingers and/or toes (x-ray diagnosis) 5. Soft tissue calcification 6. Evidence of premature atherosclerosis (e.g. history of myocardial infarction) 7. Mesenchymal neoplasms, rare neoplasms or multiple neoplasms 8. Voice changes (high-pitched, squeaky, or hoarse voice) 9. Flat feet
* Definite: All the cardinal signs and two further signs * Probable: The first three cardinal signs and any two others * Possible: Either cataracts or dermatological alterations and any four others * Exclusion: Onset of signs and symptoms before adolescence (except stature, since current data on pre-adolescent growth patterns are inadequate)

AUTHOR CONTRIBUTIONS

All authors participated in manuscript preparation. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

[1] R Foti 1, R Leonardi, R Rondinone, M Di Gangi, C Leonetti, M Canova, A Doria Scleroderma-like disorders Autoimmun Re. 2008 Feb;7(4):331-9

[2] Oshima J, Sidorova JM, Monnat RJ Jr. Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions. Ageing Res Rev. 2017 Jan;33:105-114.

[3] Oshima J, Martin GM, Hisama FM. Werner Syndrome. 2002 Dec 2 [Updated 2021 May 13]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.

[4] Goto M. Hierarchical deterioration of body systems in Werner's syndrome: implications for normal ageing. Mech Ageing Dev. 1997;98:239–254. doi: 10.1016/s0047-6374(97)00111-5.

[5] Management guideline for Werner syndrome 2020. 7. Skin ulcer associated with Werner syndrome. Geriatr Gerontol Int. 2021;21(2):153-160. Epub 2020 Nov 3.

[6] Gonullu E, Bilge NS, Kaşifoğlu T, Korkmaz C. Werner's syndrome may be lost in the shadow of the scleroderma. Rheumatol Int. 2013 May;33(5):1309-12. doi: 10.1007/s00296-012-2564-4. Epub 2012 Nov 6. PMID: 23129431.

[7] Okyar B, Akben S, Torun B, Çetin GY. A rare syndrome mimicking scleroderma: Werner syndrome. Mod Rheumatol Case Rep. 2023 Jan 3;7(1):315-319. doi: 10.1093/mrcr/rxac077. PMID: 36208300.

[8] Muftuoglu M, Oshima J, von Kobbe C, Cheng WH, Leistritz DF, Bohr VA. The clinical characteristics of Werner syndrome: molecular and biochemical diagnosis. *Hum Genet*. 2008;124(4):369-377. doi:10.1007/s00439-008-0562-0