Werner syndrome associated with acroosteolysis

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Abstract

Werner syndrome (WS) is an autosomal recessive syndrome characterized by genomic instability that affects multiple body systems. The characteristic features of the disease include growth retardation, short stature, alopecia, scleroderma, atrophic skin with ulcerations, infertility, cataracts, premature arteriolosclerosis, diabetes, osteoporosis, and increased risk of malignancies. Werner syndrome protein (WRN) protein deficiency in this disease causes changes in gene expression, similar to those observed in normal aging. As the median age of death in WS is the fourth or fifth decade of life, early diagnosis leads to a better screening opportunity for malignancies. Herein, we present a 28-year-old woman who presented with growth arrest, dyspigmentation, and acroosteolysis and was later diagnosed with Werner syndrome.

Keywords: acroosteolysis, distal phalanges, progeria, Werner syndrome

Introduction

Werner syndrome (WS) is a rare genetic disorder characterized by premature aging and follows an autosomal recessive inheritance pattern. It is commonly known as "Progeria Adultorum" and is marked by genomic instability in addition to multi-system involvement [1]. The highest incidence of Werner syndrome is reported in Japan, with an average life expectancy of 46 years [2]. Werner syndrome protein plays a significant role in telomere maintenance and its deficiency alters gene expression, causing the shortening of telomeres at an advanced pace [3]. Consequently, WS presents with varying phenotypes leading to a decline in the physiological functions of various organs [4]. Herein, we present a case of this rare syndrome with early onset of acroosteolysis.

Case Synopsis

A 28-year-old woman presented with features of growth arrest from the age of ten, resulting in low bodyweight, short stature, and slender limbs. She had also developed hypo and hyperpigmented patches, beginning from arms and extending towards the legs and abdomen, associated with thin, taut skin. The patient started experiencing a gradual loss of nails from the early age of ten, which began in the fingers of hands and feet and was followed by resorption of distal phalanges (**Figure 1**). There was a history of recurrent respiratory and urinary tract infections that gradually worsened over time.

The patient also complained of difficulty walking and wearing shoes owing to callus formation of the feet. She was diagnosed with Type 2 diabetes mellitus at the age of 18 years, for which she began anti-diabetic medication. There was no history of cataracts or skin ulcers. Her parents had a consanguineous marriage between first cousins. The patient is also married with two children. However, there were no relevant features in her siblings or children.

On examination, the patient presented an older appearance for her age. There was resorption of terminal phalanges of hands and feet with partial

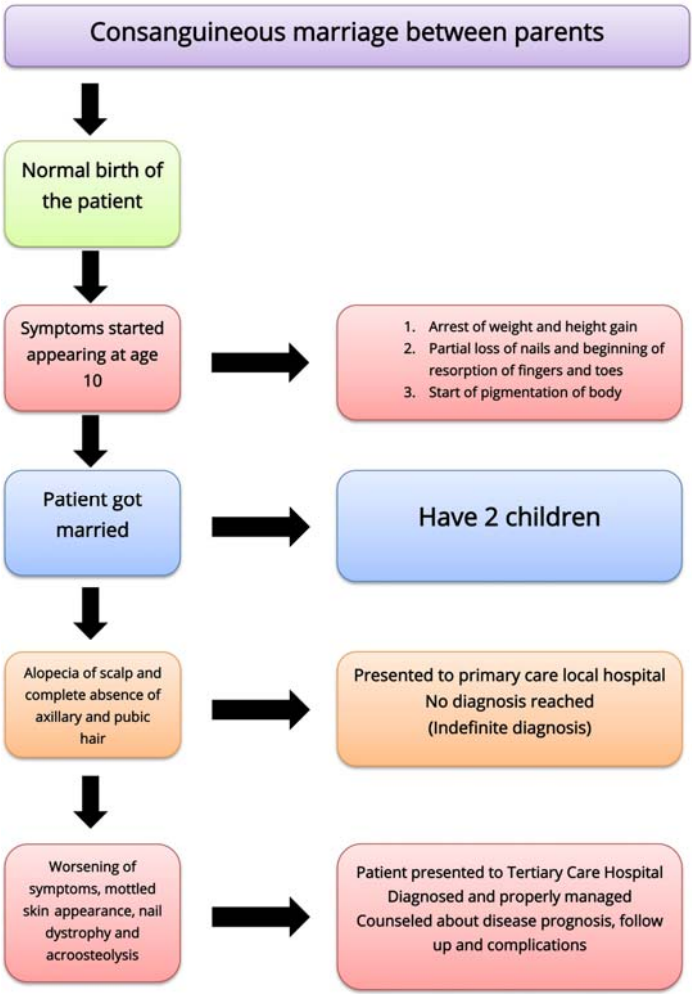

Figure 1. *The figure explains the timeline of the patient's clinical features and associated risk factors. Note that the patient is married with two children ruling out infertility.*

loss of nails and contracture formation (**Figure 2**). She exhibited short stature with a height of 4 feet, 1 inch (125cm) and a weight of 35kg. Her nose was beaked with a relatively small-sized lower jaw. The skin of the face, hands, and feet was wrinkled with evidence of scleroderma-like changes (**Figure 3A**). The hair growth was also sparse and female pattern alopecia was observed over the scalp region (**Figure 3B**) with a complete absence of pubic and axillary hair (**Figure 3C**). Mottled skin pigmentation on the abdomen, arms, and legs was also observed.

Routine laboratory investigations showed hyperglycemia, low hemoglobin of 11.1g/dl, and raised erythrocyte sedimentation rate of 33mm/hr. Liver, renal, and thyroid function tests were within normal limits. Echocardiography revealed normal biventricular systolic function with impaired relaxation of the left ventricle. Further investigations confirmed the presence of cystitis and gall stones. Radiographic examination of hands and feet confirmed the resorption of distal phalanges (acroosteolysis) and soft tissue calcific deposits close to the tips of fingers and toes with peri-articular osteoporosis (**Figure 4**). Decreased joint space at metacarpophalangeal joints was also noted. Cataracts were ruled out on slit-lamp examination and indirect laryngoscopic findings were also insignificant.

Case Discussion

Werner syndrome is an autosomal recessive disorder and careful observation of the clinical features typically leads to its diagnosis [5]. As was in our case, consanguineous marriages significantly increase the

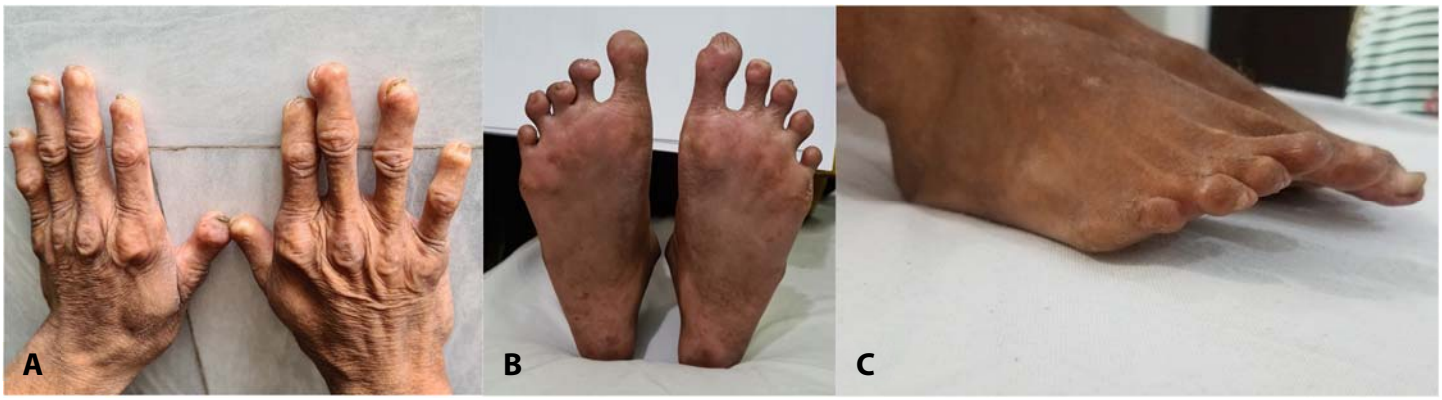

Figure 2. ***A)*** *Resorption of distal phalanges (acroosteolysis) in fingers is seen with nail dystrophy (more prominent in fingers of right hand). Atrophic skin changes and small joint involvement can also be seen.* ***B)*** *Acroosteolysis, loss of fingerprints, and callus formation on the edges are visible in toes and feet. Nail dystrophy is more prominent in the toes of the right foot.* ***C)*** *Nail dystrophy and contracture formation are clearly visible.*

Figure 3. ***A)*** *Characteristic facial features of scleroderma are visible with a beaked nose, microstomia, and radial furrowing around the mouth. The patient also shows wrinkling and an older appearance for her age.* ***B)*** *Scalp showing sparse hair in female pattern alopecia. Premature wrinkling on the face can also be observed.* ***C)*** *Mottled skin appearance with complete absence of axillary hair is evident.*

probability of WS occurrence in patients and their siblings [6,7]. We would like to emphasize the atypical feature of acroosteolysis, which is rare and started at an earlier stage than most patients with WS.

The presenting feature of WS in most patients is growth arrest followed by premature greying of hair, hypogonadism, diabetes mellitus, osteoporosis, cataracts, scleroderma, and loss of subcutaneous fat [8]. However, along with the other ongoing signs and symptoms of WS, such as growth arrest and dyspigmentation, our patient presented with additional features of acroosteolysis, absence of fingerprints, and loss of nails, which rarely become evident at early stages of this syndrome.

Her finger and nail changes began with the partial loss of nails of hands and feet, starting at an early age and then gradually progressed to complete resorption of distal phalanges. Moreover, contracture formation of the distal joints of hands and feet also followed shortly. Symptoms of WS typically appear in the third or fourth decade of life, but our patient presented at an early age of ten and gradually progressed to full-blown disease at the end of the second decade of life. The patient exhibited most of the cardinal signs and symptoms required for the diagnosis of WS according to the International Registry of Werner Syndrome except cataracts and skin ulceration [5].

Previously reported radiographic findings of WS include osteoporosis (more pronounced in the extremities and distal phalanges of hands and feet) and soft tissue calcific deposits [9,10]. Both of these features were evident on radiographs in our patient, along with decreased joint space at metacarpophalangeal joints. These findings contrast with the topography of osteoporosis in normal aging that begins in the vertebrae.

The probability of endocrine and metabolic disorders in patients with WS is significantly higher [11]. Glucose homeostasis is also impaired due to insulin resistance, leading to diabetes mellitus [12]. Alopecia is another endocrine disorder commonly present in patients with WS that involves the scalp, axillary, pubic, and in some cases, truncal hair. Our patient was diagnosed with Type 2 diabetes mellitus and alopecia of the scalp with an absence of axillary and pubic hair.

The average life expectancy in patients with WS is around 54 years [13]. The cause of death in these patients is a myocardial infarction, or malignant

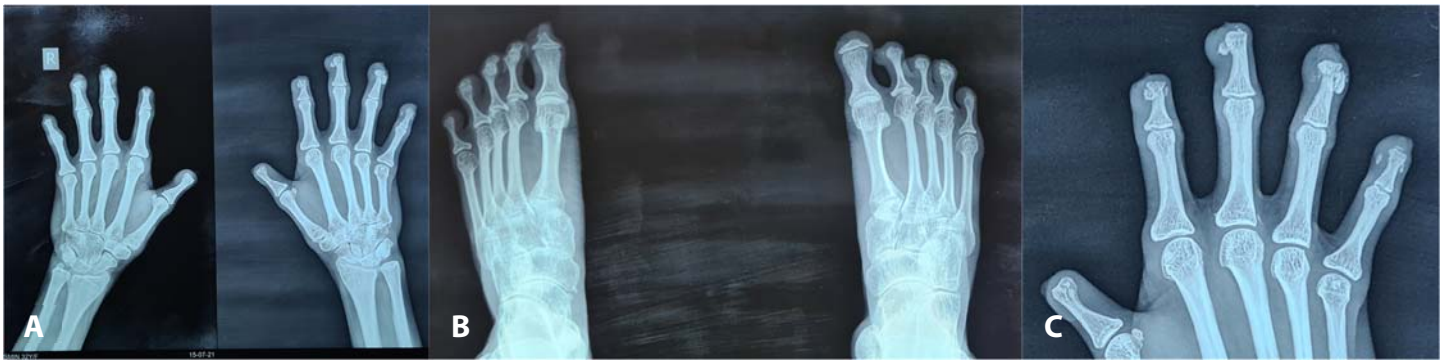

Figure 4. ***A)*** *Radiograph of hands showing acroosteolysis, soft tissue calcific deposits close to the tips, peri-articular osteoporosis, and decreased joint space at metacarpophalangeal joints.* ***B)*** *Acroosteolysis and peri-articular osteoporosis are clearly visible, more pronounced in the right foot.* ***C)*** *Close-up radiographic image demonstrating features of acroosteolysis.*

transformation, as the risk of developing malignancies is exponential [14]. Therefore, early diagnosis and periodic screening are crucial.

The patient's life was being severely affected by her skin disease as assessed by Dermatology Life Quality Index (DLQI) with a score of 25 [15]. On top of that, she had an absence of fingerprints leading to significant social struggles and inconvenience. The debilitating features of WS are associated with social stigmatization that may lead to non-adherence to medical therapy. Her interpersonal relationships were also significantly affected, leading to a further decline in her mental health.

Since there is no specific treatment for this disorder, the patient was managed symptomatically and counseled regarding the prognosis and related complications. The patient has regular follow-up, psychotherapy, and periodic malignancy screening.

Conclusion

Werner syndrome is a rare genetic disorder that presents with premature aging and involves multiple body systems. In addition to the typical features of Werner syndrome, acroosteolysis can also occur in the early stages of this syndrome. Careful examination is of paramount importance while considering the diagnosis of WS. Debilitating features of the disease lead to social struggles and decreased quality of life, making psychotherapy an effective tool in the management. Regular follow-ups, periodic screening for malignancies, and proper counseling are recommended components of the management strategy.

Potential conflicts of interest

The authors declare no conflicts of interest.

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