ASIDE Case Reports

Case Report

Rare Presentation of Werner Syndrome in a 28-Year-Old Female Patient: A Case Report and Literature Review

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ABSTRACT

Werner Syndrome (WS) is a rare autosomal recessive disorder characterized by accelerated aging and a broad spectrum of clinical manifestations. This case report presents a unique instance of WS from Pakistan, featuring a novel mutation in the WRN gene. Known as progeria adultorum, WS typically manifests post-pubertally due to mutations in the WRN gene, which plays a key role in DNA repair and genomic maintenance.

A 28-year-old woman presented with non-healing bilateral leg ulcers, dry skin, and photopsia. She exhibited multiple signs of premature aging, including short stature, early hair graying, and bilateral cataracts. Her medical history included hypothyroidism, cataract surgery, and recurrent gastrointestinal infections. Genetic testing confirmed a homozygous pathogenic variant in the WRN gene, thereby establishing the diagnosis of WS.

This case highlights the diagnostic challenges associated with rare genetic syndromes. The patient's diverse clinical signs—such as persistent ulcers, cataracts, and failure to experience a pubertal growth spurt—were consistent with diagnostic criteria for WS. The report explores the pathophysiology of WS, particularly the role of WRN mutations in impaired DNA repair and increased genomic instability, which significantly elevates cancer risk.

There is currently no specific treatment for WS; management remains supportive, focusing mainly on symptomatic relief. This case emphasizes the importance of early recognition, targeted genetic testing, and multidisciplinary care. Greater awareness and understanding of WS are essential for timely diagnosis and intervention. Furthermore, ongoing genetic research may offer valuable insights into disease mechanisms and potential therapeutic strategies, ultimately aiming to improve patient outcomes.

1. Introduction

Werner Syndrome is a rare autosomal recessive disorder characterized by accelerated aging and a constellation of clinical manifestations. Typically, it involves premature graying of hair, short stature, and joint stiffness. In this case report, we present a unique instance of Werner's syndrome (WS) originating from Pakistan, showcasing a novel mutation. WS, also known as progeria adultorum, is an autosomal recessive disorder that expedites the aging process shortly after puberty [1]. This condition emerges due to mutations within the WRN gene, which is responsible for encoding a member of the RECQ DNA helicase family, crucial for DNA repair mechanisms [2]. The hallmark features of WS encompass not only genomic instability but also the premature onset of an array of age-related ailments, such as ocular cataracts, senile appearance, diabetes mellitus, dyslipidemia, osteoporosis, arteriosclerosis, and malignancies [3, 4].

Recent insights have led to a more nuanced understanding of WS. Rather than purely accelerating aging, the absence of WRN protein appears to trigger a comprehensive decline in the regular physiological functions across diverse organs [3]. This reevaluation highlights the broader implications of the absence of WRN protein on overall health. In light of these considerations, our report examines a rare occurrence of WS, characterized by an innovative mutation originating from Pakistan.

2. Case Presentation

A 28-year-old woman presented to the medical outpatient department with persistent concerns surrounding a non-healing ulcer located on her bilateral shins and ankle region, a condition that had persisted for two months. Concurrently,

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she also experienced sensations of dry skin and persistent itching, along with occurrences of flashing lights in her eyes. The patient noted that her physical development progressed typically until the age of 10. However, subsequent to this period, her stature and weight ceased to increase, and she experienced an early onset of hair graying. No further medical workup was performed at age 10 when growth cessation was noted.

At the age of 16, she received a diagnosis of primary hypothyroidism, leading to continuous medical treatment with weight-based dosage of exogenous levothyroxine at 1 mcg per kg. Additionally, she encountered the development of cataracts in both eyes by the age of 25, necessitating surgical intervention for bilateral removal of cataracts. No further workup was done at that time. The patient disclosed a history marked by recurrent gastrointestinal infections (leading to symptoms of watery diarrhea for 2 weeks) every 1 or 2 months, and a decade following her entry into puberty at age 17, she noted a gradual thinning of her voice. She was empirically treated for the gastrointestinal infections with metronidazole and supportive management, and no further workup was done to identify the specific organisms. She remained unmarried and without any offspring.

Approximately four months prior to her presentation, she encountered an itchy rash on her lower leg and ankle. Persistent scratching led to the formation of an ulcer in the affected region. A thorough clinical assessment unveiled several distinctive features, including a prematurely aged appearance, limited height, parched skin, diminished hair volume, taut skin accompanied by subcutaneous atrophy, and lips displaying pursed contours with furrowing, as shown in **(Figure 1)**.

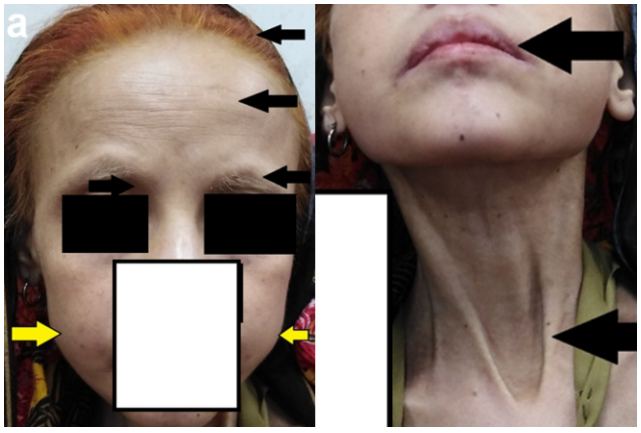

Figure 1: (a) Upper arrows (black) pointing to graying and blonding of hair and eyebrows, while the lower arrows (yellow) point to the maxillary hyperplasia seen in our patient. (b) Upper black arrow (black) pointing towards cracked lips and lower arrow (black) pointing to the significant wasting seen in our patient.

Further physical examination revealed well-defined tender ulcers, characterized by hyperkeratotic borders, situated over the region encompassing the bilateral lower legs, as shown in **(Figure 2)**. The ulcer's floor exhibited pale granulation tissue along with a clear discharge, while the surrounding skin displayed signs of erythema indicative of eczematous changes. Notably, significant limb wasting was also observed.

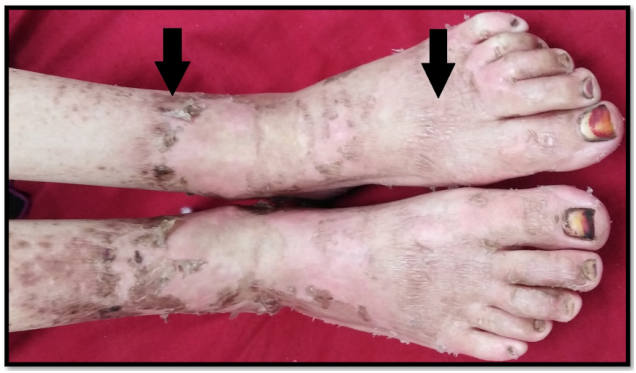

Figure 2: Extensive scaling and desquamation after ulcer resolution on bilateral legs, ankles, and feet region, seen in our patients.

Routine investigations, including hormone assessments, yielded results within typical ranges. However, the patient's thyroid-stimulating hormone levels were elevated (34 mIU/L), suggesting uncontrolled hypothyroidism (since her 1 mcg per kg dose was way below the recommended dosage of 1.6 mcg per kg), which was then subsequently corrected to the recommended dose. A biopsy of the ulcer was conducted, yielding no indications of dysplasia or malignancy. Radiographic evaluation of the foot disclosed indications of osteoporosis as shown in **(Figure 3)**.

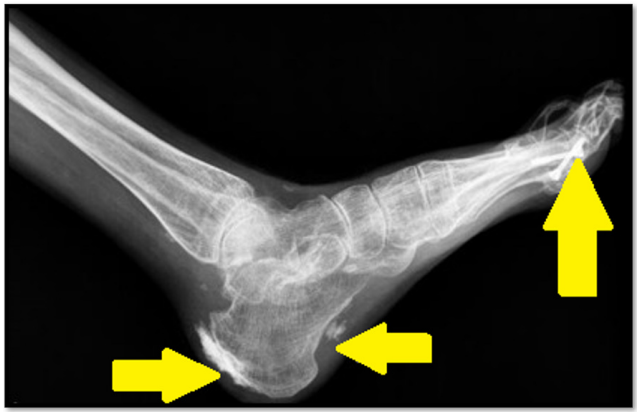

Figure 3: Lateral foot x-ray showing evidence of osteosclerosis in the proximal interphalangeal joint (yellow right-sided arrow); soft tissue calcification at the posterior calcaneal region (yellow right-sided arrow) and osteoporotic lesions at the inferior calcaneal regions (yellow left-sided arrow) seen in our patient.

Conducting genetic analysis in accordance with the International Registry of Werner Syndrome revealed a substitution mutation characterized by a homozygous pathogenic variant c.3190 C>T in exon 26 of the WRN gene [5, 6]. This finding was subsequently verified through Sanger sequencing. The patient received comprehensive counseling regarding her condition and its potential long-term ramifications. She

currently remains under regular surveillance to enable the early detection of cutaneous malignancies and cardiovascular complications. Follow-up a month after the change in levothyroxine dosage revealed a trend towards lowering of the TSH to 15 mIU/L along with improvement of the hypothyroidism symptoms, suggesting that a therapeutic dose was being delivered to the patient.

3. Discussion

This case serves as a quintessential illustration of the intricate diagnostic journey required to uncover rare genetic disorders. The initial presentation of left leg ulcers, fever, and joint pain was enigmatic, necessitating a sequential exclusion of common causes.

When evaluating a patient with suspected Werner Syndrome (WS), several differential diagnoses must be considered due to overlapping clinical features. Hutchinson-Gilford Progeria Syndrome (HGPS) is a notable progeroid disorder that presents in early childhood with growth retardation and cardiovascular complications. Still, it lacks cataracts and typically has an earlier onset than WS [7]. Rothmund-Thomson Syndrome (RTS) may resemble WS due to features like cataracts and increased cancer risk; however, its hallmark findings include poikiloderma and skeletal anomalies [8]. Cockayne Syndrome also presents with growth failure and premature aging, but is distinguished by early-onset neurodevelopmental delay and photosensitivity [9]. Bloom Syndrome is characterized by short stature, photosensitive rash, and chromosomal instability, yet lacks the accelerated aging and ocular involvement seen in WS [10]. Systemic sclerosis can mimic WS with features such as skin tightening and chronic ulcers, but it is an autoimmune condition that is identifiable by serologic markers and internal organ involvement [11]. Mandibuloacral dysplasia, a laminopathy, shares traits such as lipodystrophy and skeletal abnormalities, but is differentiated by its distinctive craniofacial and metabolic features [12]. Careful clinical evaluation and genetic testing are crucial for distinguishing WS from these overlapping syndromes. Genetic testing, ultimately revealing mutations in the WRN gene, unveiled the rare genetic etiology. Radiographic findings further aligned with the clinical presentation, underscoring the complexity and diversity of Werner Syndrome's manifestations.

Werner's syndrome (WS) is a genetic disorder inherited in an autosomal recessive manner, first elucidated by Otto Werner, a German physician, in 1904. His initial account detailed four instances of siblings displaying symptoms like juvenile cataracts, scleroderma-like alterations in their extremities, stunted growth, premature aging of facial features, graying hair, and hypogonadism [13, 14]. Cases of WS have emerged across various populations, with a particularly pronounced prevalence observed in Japan (with an estimated occurrence of 1 in 100,000) and the Sardinia province of Italy [15, 16]. A salient initial sign often noticed is the absence of the anticipated growth spurt during puberty, a phenomenon evident in our case. An almost ubiquitous observation in WS is the presence of bilateral cataracts

Table 1: Application of the diagnostic criteria of the International Registry of Werner Syndrome in our patient.

Cardinal Signs and Symptoms	Present Case
Cataract (bilateral)	Present
Short stature	Present
Characteristic dermatological pathology	Present
Parental consanguinity	Present
Premature graying and/or thinning of scalp hair	Present
Diabetes mellitus	Absent
Hypogonadism	Present
Osteosclerosis of the distal phalanges of the digits	Present
Osteoporosis	Present
Soft tissue calcification	Present
Voice changes	Present
Flat feet	Present
Evidence of premature atherosclerosis	Absent
Any mesenchymal/rare/multiple neoplasms	Absent

in conjunction with non-healing ulcers affecting the lower legs region. Other clinical attributes include skin atrophy, a pinched facial appearance, thin and gray hair, a hoarse voice, diabetes, atherosclerosis, skin ulcers, hypogonadism, and osteoporosis. Malignancy and myocardial infarction emerge as the most prevalent causes of death in the fifth decade of life [3]. Among WS patients, the most commonly reported malignancies comprise thyroid carcinomas (16%), followed by melanoma, soft tissue sarcomas, and leukemia [17]. Our patient's diagnosis of WS aligns with the diagnostic criteria laid out by the International Registry of Werner Syndrome (IRWS) as presented in **(Table 1)** [18].

The presence of homozygous or compound heterozygous loss-of-function mutations in the WRN gene underpins Classic WS. WRN localizes within the nucleolus, translocating to the site of DNA strand breaks. Evidence suggests that WRN engages in various cellular processes, including DNA replication, recombination, and repair, telomere maintenance, transcription, mitochondrial function, and epigenetic alterations. In a proliferating cell, the WRN protein displays affinity for specific substrates like G4 quadruplexes, holiday junctions, and bubble structures, facilitating its role in DNA repair [18]. To date, approximately 86 distinct WRN mutations have been documented. These have been succinctly reviewed by Yokote et al. and other sources [19, 6]. Most of these mutations involve stop codons, which can potentially result in the loss of nuclear localization of the WRN protein. Consequently, the mutated WRN protein fails to access the nucleus [20]. The WRN gene promotes genomic stability and DNA repair, rendering WS patients predisposed to various forms of cancer. Notably, C-terminal WRN mutations have been closely linked to follicular thyroid carcinoma [21].

Regrettably, no specific treatments targeting WS are presently available. Nonetheless, ongoing research explores novel therapeutic avenues, including p38 mitogen-activated protein kinase inhibitors with implications for aging and age-related ailments [22]. Managing WS typically involves

symptomatic treatments tailored to individual organ involvement, whereas addressing non-healing cutaneous ulcers requires a proactive approach.

4. Conclusion

This case report sheds light on the intricate clinical phenotype and genetic basis of Werner syndrome (WS), highlighting the diverse range of symptoms that encompass premature aging, cataracts, skin atrophy, and non-healing ulcers. The discovery of a novel homozygous pathogenic variant within the WRN gene underscores the genetic heterogeneity of WS. Unilateral chronic ulcers in the lower legs, along with vision abnormalities, should awaken a clinician to the possibility of this syndrome as one of the differential diagnoses. The case underscores the need for heightened awareness, early diagnosis, and comprehensive management strategies for WS patients, while also highlighting the ongoing significance of genetic research to deepen our understanding of this complex disorder and potentially inform future therapeutic avenues.

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

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Informed consent

Before inclusion in the study, written informed consent was obtained from the patient.

Large Language Model

No large language models (LLMs) were used in manuscript preparation.

Authors Contribution

MS contributed to conceptualization, methodology, data collection, software, original manuscript drafting, and visualization; MI contributed to conceptualization, methodology, data collection, data curation, writing the original manuscript draft, and validation; KA contributed to conceptualization, data collection, data analysis and interpretation, and writing—reviewing and editing; AA and UB contributed to supervision, funding acquisition, project administration, manuscript review, and editing.

Data Availability

Data supporting the findings of this study are not publicly available but can be obtained from the corresponding author upon reasonable request.

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