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Interstitial lung disease in a patient with premature aging: Suspected Werner syndrome

Greisha M Gonzalez-Santiago, Ricardo Fernandez-Gonzalez, Modesto Gonzalez-Del Rosario, Radames Sierra-Zorita, Carlos D Garcia

ABSTRACT

Werner syndrome (WS) is a rare inherited autosomal recessive disease that can be diagnosed with cardinal signs without the genetic testing. Some features that are consistent with WS include premature aging, loss, and graying hair, scleroderma-like skin changes. We report a 42-year-old man with cardinal signs of WS who also developed interstitial lung disease (ILD). The patient had past medical history (PMHx) of atypical left femur fracture in his early 30s from unknown causes. Also, he had loss and graying hair, salt-on-pepper skin changes, associated with squeaky voice, muscle wasting, and osteoporosis. He had worsening symptoms of dyspnea on exertion and was found with bilateral diffuse subpleural reticular opacities with slight mid- to lower-lung predominance and mild bronchiectasis without honeycombing or ground-glass airspace opacities on chest computed tomography (CT) scan. Other causes of ILD were excluded as patient routine laboratories and rheumatologic workup was negative. Werner syndrome presents similar features with other telomerase-associated diseases such as mutations of telomerase complexes [telomerase RNA component (TERC) and telomerase reverse transcriptase (TERT)]. Werner syndrome can be difficult to diagnose because it is a rare genetic disease that begins to show symptoms and signs after 10 or 20-year-olds, but the diagnosis is recognized after 30s. Few cases have been reported about the association of WS and ILD, but both diseases are aging diseases. This case might be the first case reported in Puerto Rico of Werner syndrome associated with ILD. Early referral and treatment is important to improve patients' quality of life and life expectancy by slowing the progression of the disease.

Keywords: Interstitial lung disease, Rapid aging, Telomerase reverse transcriptase and telomerase RNA component, Werner syndrome

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INTRODUCTION

Werner syndrome is an autosomal recessive-inherited disorder that can be diagnosed without genetic testing. It can be identified, among other signs and symptoms, due to findings of premature aging, including loss and graying hair, scleroderma-like skin changes and osteoporosis in young adults in their early 30s [1]. The diagnosis can be established by the identification of cardinal signs and genetic testing should be considered when the clinical features do not confirm the diagnosis [2]. The patient's mean age is 54 years, with myocardial infarction listed as the most common cause of death, followed by malignancies including lung cancer. Few cases have been reported about interstitial lung disease (ILD) associated

with Werner syndrome. Some genetic mutations in genes encoding for components of the telomerase reverse transcriptase (TERT) and telomerase RNA component (TERT) have been associated with ILD [3].

CASE REPORT

A 42-year-old man with a history of left femoral midshaft fracture in his early 30s from unknown causes. He was evaluated by a rheumatologist due to this pathologic fracture, and the patient was lost to follow-up for almost 10 years. Then, he was being evaluated by a pulmonologist due to worsening symptoms of dyspnea on exertion in the last three months. Subsequently, he was found with bilateral diffuse subpleural reticular opacities with slight mid- to lower-lung predominance and mild bronchiectasis and bronchiolectasia without honeycombing or ground-glass airspace opacities on chest CT scan, consistent with usual interstitial pneumonia (Figure 1). Pulmonary function test presented with forced vital capacity 1.84 L (45%), FEV1/FVC 76%, FEV1 43, total lung capacity 115 L, residual volume/total lung capacity 72%, diffusing capacity for carbon monoxide 96%. After 10 years of absence, the rheumatologist noticed rapid aging of the patient and physical features that were unusual for this patient's age. He had premature graying and hair loss of the scalp and eyebrow that began in his 20s, wasting of his hand muscles, legs, and femur, squeaky voice, and salt-on-pepper marble-like look of the skin on his upper back (Figure 2). Laboratories including white blood cells, hemoglobin (Hgb), hematocrit (Hct), platelets, and renal function tests which were within normal limits. Rheumatologic work-up was essentially negative. Bone scan from 2009 showed focally increased activity in the midshaft of both femora anterolateral aspects, diffusely increased peri-cortical uptake along the anteromedial aspect of the left femur and mild in the right femur distal metaphyseal area. There was mild increased peri-cortical uptake in the distal shaft of the right tibia without focalization. Increased peri-cortical uptake was also observed in the distal shaft anterior aspect of the left humerus. A 2012 bone scan showed an intense tracer concentration in the left femoral midshaft at the known fracture site. In addition, there was an area of intense activity at the proximal shaft, lateral aspect related to a known fixation screw. There was a focal area of increased peri-cortical activity in the right femur (Figure 3). Additionally, a dual-energy X-ray absorptiometry (DEXA) scan performed on 2021 bone mineral density (BMD) measured total femur BMD of 0.779 g/cm^2 with a T-score of −2.2 and a Z-score of −2.0, this patient had a very low BMD for his age and sex and on this basis he was diagnosed with osteoporosis at age 42 (Figure 4). Unfortunately, the patient's condition worsened, requiring multiple hospitalizations due to dyspnea which required home oxygen while being treated with Nintedanib (OFEV) for his interstitial parenchymal changes. The patient's Werner diagnosis was not confirmed by genetic studies.

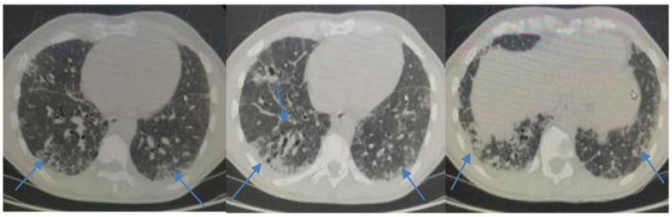

Figure 1: Bilateral diffuse subpleural reticular opacities with slight mid- to lower-lung predominance, mild bronchiectasis, and bronchiolectasis.

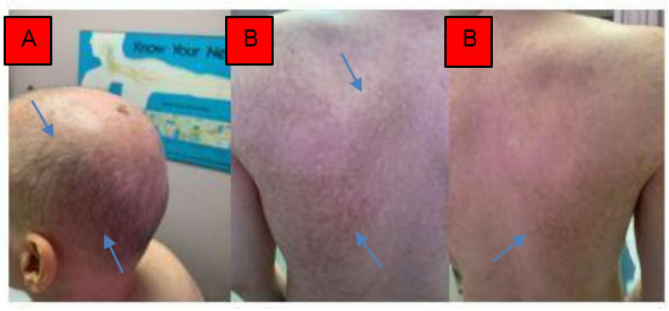

Figure 2: (A) Graying and hair loss and (B) salt-on-pepper (scleroderma-like skin changes).

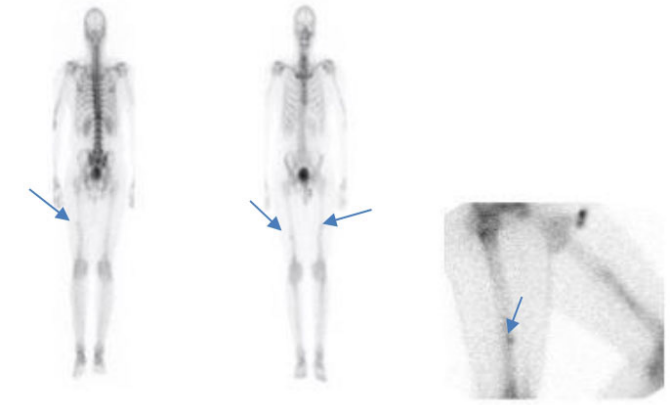

Figure 3: Increased activity in the midshaft of both femora anterolateral aspects, diffusely increased peri-cortical uptake along the anteromedial aspect of the left femur and mild in the right femur distal metaphyseal area. Increased peri-cortical uptake is also observed in the left humerus distal shaft anterior aspect.

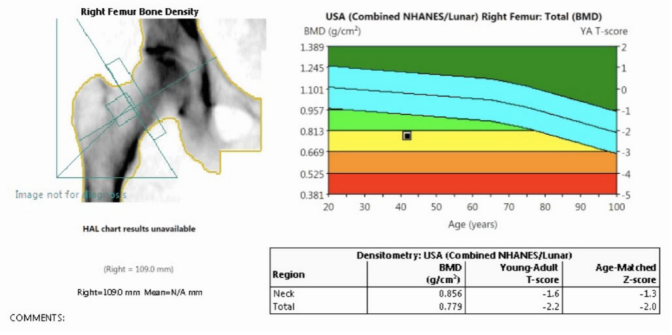

Figure 4: Femur total is 0.779 g/cm^2 with T-score of −2.2 and Z-score of −2.0, this patient has very low BMD for their age and sex.

DISCUSSION

Werner syndrome can be difficult to diagnose because it is a rare genetic disorder that usually begins to manifest symptoms after 10 or 20 years of age, but the diagnosis is usually recognized after 30 years [4]. In the presence of cardinal symptoms such as loss of and graying hair, bilateral cataracts, voice changes, osteoporosis, premature aging, short stature, and scleroderma-like skin changes, the diagnosis can be made even without genetic testing [5]. On the other hand, few cases have been reported on the association of Werner syndrome with ILD. Werner syndrome presents common features with other telomerase-associated diseases such as mutation of telomerase RNA component (TERC) and telomerase reverse transcriptase (TERT) [6, 7]. Also, familial and sporadic cases of ILD have been associated with those mutations. Other causes such as drugs, smoking, and connective tissue disease (CTD) were excluded in our patient. Our patient's chest CT suggested a usual interstitial pneumonia (UIP) pattern that correlates with severe pulmonary fibrosis. Even though genetic studies were not performed to confirm the diagnosis in our patient, his cardinal symptoms, and the presence of ILD increase the concern of Werner syndrome's association with pulmonary fibrosis. Both Werner and ILD are premature aging diseases, and overall aging of the body and lung, respectively. The mean age of patients with Werner syndrome is 52.8 years and ILD usually appears after 54 years which makes the diagnosis of ILD in Werner syndrome difficult. But in our patient ILD symptoms started in his early 40s.

CONCLUSION

This case report is limited because genetic studies were not performed, since his compliance was very poor. However, as mentioned above, this genetic test is not necessary for the diagnosis if the patient has the cardinal physical findings. In conclusion, this case might be the first case report in Puerto Rico of Werner syndrome associated with ILD at a younger age than usual in a no-smoker patient. We should keep in mind that early referral and initiation of new treatment options in patients with ILD can increase life expectancy and slow the disease progression.

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Author Contributions

Greisha M Gonzalez-Santiago – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ricardo Fernandez-Gonzalez – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Modesto Gonzalez-Del Rosario – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Radames Sierra-Zorita – Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Carlos D Garcia – Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the

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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.