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Complex CAD with No Cardiac Risk Factors Revealing a Werner Syndrome Diagnosis in 52 Year Old Moroccan Male, (An Original Case report of Cardiology Department at Casablanca University Hospital, Morocco)

S. Belkouchia, Z. Ammouri, S. Zahri, E. Rochd, M. Bouziane, M.H Aboub, S. Arous, G. Benouna, A. Drighil, R. Habbal

Casablanca University Hospital, Morocco

Werner syndrome (WS), also called premature aging, is a very rare genetic disorder with autosomal recessive inheritance, which is characterized not only by premature aging but also by an increased risk of cardiovascular diseases and cancer (8). This case report talks about a 52-year-old man, with angina pectoris episodes exertion-induced and with stress test findings positive, who was diagnosed with CAD in non-diabetic, non-smoking status with conventional cardiovascular risk factors rare. The subsequent diagnostic studies including TTE and coronary angiography revealed very severe, multi-vessel disease. The complete genetic study proved that the diagnosis of Werner's Syndrome was true, through the search for a homozygous mutation in the WRN gene (9). The patient treatment scheme involves medical treatment for ischemic heart disease as well as coronary artery bypass grafting referral. This study emphasizes the crucial need to think about the WS in patients having atypical CAD symptoms and thus realizing the importance of awareness among the clinical staff to detect clues that point to WS for quick diagnosis and management.

Introduction

Coronary artery disease (CAD) is one of the main factors responsible for a huge number of deaths and cardiovascular disorders globally. It arises due to development of atherosclerotic plaques in the coronary arteries (main blood vessels supplying the heart), which may cause occlusion and may lead to angina and myocardial infarction (1). The conventional risk factors include hypertension, hyperlipidemia, smoking, diabetes, and a family history of cardiovascular disease. On the other hand, WS is a genetic disease which is caused because of autosomal recessive inheritance pattern and is characterized with the features of early aging and malignancies and cardiovascular disorders. It is generated by the WRN gene mutations caused by impairment of DNA repair and genome stability (8). TWG usually develops cataracts, scleroderma-like skin lesions, and dwarfism phenotypes; however, its connection to early-onset coronary artery disease is uncommon and underappreciated. This case is of particular interest as the patient, a 52-year-old male with no typical CAD risk factors, exhibits an abnormal presentation of Werner Syndrome represented in the fact of significant coronary artery involvement, the atypical picture of this rare syndrome regarding the known characteristics of the same (2).

Case Presentation

A 52-year-old man with a history of scleroderma came to the clinic, and the pain in the chest became worse during physical activity. What is particularly noteworthy here is that this patient had none of the classical cardiovascular risk factors like diabetes, smoking, or family history of coronary artery disease. Before the retroelement, he had been submitted to surgery for bilateral cataract at the age of 28, an extremely early medical intervention that could hint at pathology. Our case was an atypical one - a patient who had been diagnosed with peripheral arterial disease (PAD) up until then, had no contributory factors of either lifestyle or systemic factors that are usually seen in vascular pathologies (4).

Upon clinical examination, the patient presented several distinctive physical characteristics: a short stature of 155cm (about 5.09 ft), thin hair of white color, a thin voice, and a specific-looking face, The discoveries soon moved beyond the primary diagnosis, and soon after, peripheral arterial disease, towards deep-rooted genetic conditions that might be responsible. The presence of our internist colleagues was instrumental in tackling the problem at this point. We were relieved by the fact that scleroderma was dismissed through their process so the genetic discovery in which we were interested was already pinpointed. The initial clinical observation that was different from scleroderma symptoms suggested the possibility of a different diagnosis by the physician. The hypothesis was tested later by genetic testing, which revealed that the patients had a homozygous mutation of the WRN gene.


Fig 1: Characteristics facial features of Werner Syndrome

The exertional angina was the most severe in terms of physical limitation on the patient's activities, since it was happening even at the ordinary level of exertion or at times even at rest. CCS classifies angina into III. The results of the stress test were positive, indicating a very high probability that someone had significant narrowing of the coronary arteries. That incited the doctor's desire for additional study on the etiology of the patient's symptoms and the assessment of possible conditions that might be silent or not was recognized as the contributing factors towards the patient's clinical presentation.

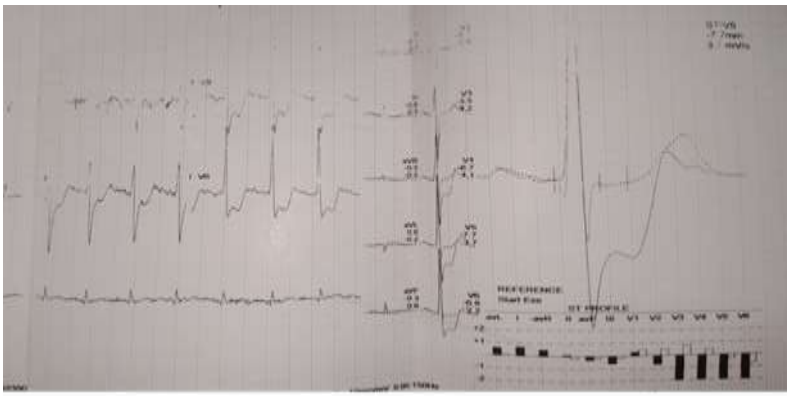

Figure2: Positive Stress EKG

Since our patient had a history of scleroderma and after finding the fact of PAD, the development of exertional angina is potentially serious. It has opened a wide exploration for the possible cardiovascular involvement, providing a unique journey, that started from differential diagnosis and ended very unexpectedly and insightfully.

Investigations

Rest EKG was normal, transthoracic echocardiography (TTE) demonstrated no evidence of left ventricular dilatation or hypertrophy, patient having an ejection fraction of 65%, suggesting normal systolic function. the valvular problems noted were minimal mitral regurgitation with a slightly calcified mitral annulus but without significant mitral stenosis and a calcified aortic valve with minimal aortic regurgitation and no stenosis. From the dimensions of the cardiac chambers, along with the pulmonary artery pressures, the result was normal and there was no sign of increased pulmonary artery pressures.

Laboratory studies showed a hemoglobin level and white blood cell count to be normal and had a Negative Troponin level, CRP of 7 mg/L, which could signify either inflammation or atherosclerosis (3). Laboratory tests for kidney function along with liver enzymes were within the normal limits, and there was nothing concerning common systemic conditions implicated in cardiovascular disease.

The breakthrough to diagnosis came after gene studies' results were in. Consequently, molecular examination disclosed a homozygous mutation in the WRN gene, which manifested the diagnosis of Werner Syndrome (9). The clinical picture, which was highly suggestive of progeria, a very complex genetic syndrome characterized by premature aging accompanied by multisystem involvement, provided a plausible explanation for the patient's premature vascular aging as multi- vessel coronary artery disease. The arrest of classical cardiovascular risk factors plus the genetically revealed results confirmed it as a special case of coronary artery disease due to Werner Syndrome. Thus, the role of Werner Syndrome in coronary artery disease pathogenesis has been reaffirmed.

Here's the patient's clinical findings and diagnostic results displayed as a table:

Parameter	**Findings**
Demographics	52-year-old male

	Non-diabetic, non-smoker
Medical History	Unconfirmed Scleroderma for 6 years Bilateral cataract surgery at age 28 Peripheral arterial disease recurrent skin ulceration
Clinical Presentation	Exertional angina, CCS Class III Positive stress test
Echocardiography Findings	Ejection fraction: 65% LV dimensions: normal Mild mitral insufficiency without stenosis (Calcified annulus) Minimal aortic insufficiency (Calcified valve)
Laboratory Results	CRP: 7 mg/L Troponin : Negative Hemoglobin: Normal WBC: Normal Renal and liver function: Normal
Genetic Study	Homozygous mutation in WRN gene Confirmed diagnosis of Werner Syndrome

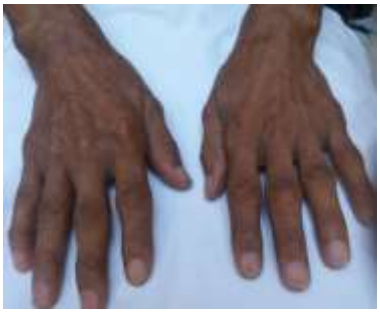
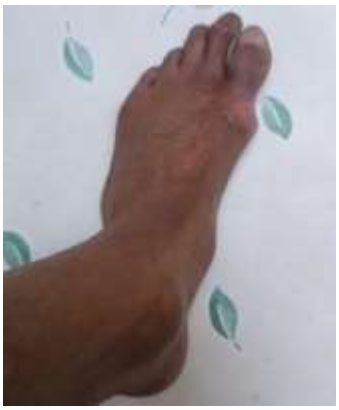
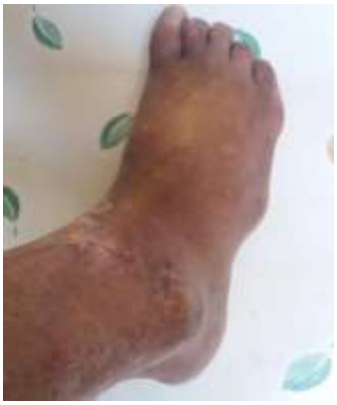

Figure 3, 4,5 : Scleroderma-Like kin lesions

Discussion

Werner syndrome (WS) is a rare disease that causes early aging and increases the risk of aging disorders like atherosclerosis and cancer. Mutations in the WRN gene cause WS, indicating the RecQ Helicase, which repairs DNA and stabilizes genomics. Deficient WRN protein activity accelerates cellular aging and increases DNA damage, causing age-related diseases early (5).

Numerous studies have linked Werner syndrome to progressive atherosclerosis. Williams syndrome patients are diagnosed with cardiovascular illness at a younger age, including atherosclerosis, which is rare in the community. ST's accelerated aging, which is sensitive, may cause atherosclerotic plaques to grow early. Research shows that WS patients have elevated oxidative stress and inflammation, which are linked to atherosclerosis.2013; 8: 1023-32】
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Werner Syndrome adds a unique perspective to the atypical course of coronary artery disease (CAD). Despite not having diabetes, smoking, or a family history of CAD, the patient's genetics leave him susceptible to premature vascular aging. This incidence highlights the involvement of genes in CAD etiology, as WS participants are more susceptible (6,7).

The main causes of chronic adult disease (CAD) in society are lifestyle and environment, according to research. Werner syndrome is genetically dominant but not less. WS atherosclerosis is early and widespread, unlike cervical artery disease atherosclerosis. This difference is offset by the importance of genetic illnesses in diagnosing unusual or atypical cardiovascular diseases.

Genetics plays a major impact in the development of prevalent diseases such coronary artery disease, as shown by Wrinkly Reward syndrome. Establishing the link between WS and early arteriosclerosis expands our understanding of CAD pathogenesis and strengthens diagnosis in patients with unusual symptoms. Correct early diagnosis and specific cardiovascular risk management in Werner Syndrome patients show that genetics and cardiology intersect in clinical practice (2,3).

Management

The approach used to manage the patient who has been diagnosed with Werner Syndrome (WS) and simultaneous multi-vessel coronary artery disease (CAD) is comprehensive therapeutic protocol which is aimed at both alleviation of the acute heart ischemic symptoms and the surgical intervention to address the atherosclerosis. Treatment given to the patient involves pharmacotherapy directed at preventing ischemic symptoms that may continue to develop and relaxing atherosclerotic progression along with CABG as definitive measure.

As far as pharmacologically is concerned, the patient has been prescribed a regimen involving antiplatelet therapy of Apirin 75mg daily to prevent the formation of platelets clots. The administration of a drug Rosuvastatin 20mg daily has already been started to control the dyslipidemia which is one of the key risk factors of atherosclerosis. Nebivolol 5mg has been prescribed 1/4 tablet daily for blood pressure control and also as part of Perindopril 4mg once daily which is taken daily to further reduce the myocardial oxygen demand. Trimétazidine 35mg is prescribed twice a day on addition of its use to enhance coronary blood flow.

The clear indication to CABS comes from the fact that the patient has a low surgical risk and severe stenosis of LM, LAD and LCX artery a very wide territory, with enough obstruction that medical therapy and percutaneous interventions cannot take it away. Consequently, to the multi-vessel disease and the opportunity of increased quality of life and survival, CABG can be used due to its direct effects of improving myocardial perfusion. In this aspect, the surgical option is especially appropriate as the patient's WS may give rise to a faster pace of progression of vascular diseases (1,10).

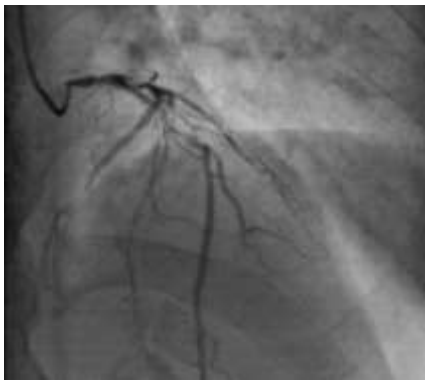

Figure 6: Coronarography results

Comprehensive multi-disciplinary plan emphasizes equally the urgent conventional CAD and the comprehensive care challenges posed by the inherited genetic condition. In a nutshell, the main goal of the approach is not only to relieve the symptoms but to do prophylactic management of cardiovascular risks by customizing the treatment to vulnerabilities of Werner syndrome.

Conclusion

The case study reveals that a middle-aged individual with no cardiovascular risk factors can exhibit the rare presentation of Werner Syndrome (WS), characterized by multivessel CAD. The identification of the homozygous mutation in the WRN gene was consistent with the diagnosis of arteriosclerosis which was ascribed to the gene mutation as a main factor in the causation of high blood pressure (common condition). Such clinical presentation exemplifies the need for comprehensive etiological investigations to help physicians to consider a wide and rare genetic differential diagnosis (2,9). The treatment plan, including pharmacotherapy and surgical interventions, illustrates the personalized purpose required to deal with complex cases where genetic disorders mix with primary cardiovascular diseases. Generally, this report will add to the literature on WS and CAD while pointing at the need for scientific awareness and understanding of the effects of genetic factors on cardiovascular health. Furthermore, it recommends giving more consideration to the pathways binding CVD to WS with the main objective to enhance the methods for diagnostics, management, and outcomes of patients with rare genetic conditions presenting CVD symptoms.

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