

Werner syndrome: A case report and review of literature

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Abstract Werner's syndrome is a rare inherited disorder characterized by short stature, sclerosed skin, cataract and premature aging of the face. The disease involves multiple systems of the body and some of the abnormalities may cause life threatening complications such as myocardial infarction and malignancy. We report a case of this rare disorder.

Key words

Pangeria, Werner syndrome, progeria adulatorum.

Introduction

Werner syndrome (WS) is considered one of the classical inherited premature aging and genomic instability syndromes.^{1,2} It is an autosomal recessive disorder affecting the connective tissue of the whole body. It is also known as pangeria and progeria adulatorum. Its clinical manifestations are short stature, scleroderma-like skin changes, cataract, and premature aging of the face.³

The highest incidence of WS reported is in Japanese patients (1000 of the around 1300 cases reported worldwide).^{4,5} This disease occurs with equal frequency in males and females.^{4,6,7} We report a case of a 32-year-old male of this syndrome who presented to us in Jinnah Hospital, Lahore for the treatment of a chronic painful ulcer over the left malleolus.

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Case report

A 32-year-old unmarried male presented with premature greying and loss of hair which started at the age of 20 years along with the history of bilateral cataract for which he was operated at the age of 21 years. Eight years later he developed corneal opacity of the right eye. There was also history of arthralgias, distal digital joint contractures and skin thickening from the age of 25 years which gradually worsened. Patient also had hypogonadism.

He developed a painful, persistent non-healing ulcer about 3 cm of diameter over the lateral malleolus of the left leg for the last 2 years. There was no history of diabetes, osteoporosis, hoarseness or high-pitched voice or any psychiatric disturbance. Rest of the systemic review was insignificant. The patient was born of a consanguineous marriage and his parents were normal. However, two of his siblings, a brother aged 28 years and sister aged 20 years, were affected with similar disease.

On physical examination, patient appeared much older than his stated age and weighed 36 kg



Figure 1 Spindly legs of patient with shiny atrophied skin.



Figure 2 Both feet showing contractures and nail dystrophy.



Figure 3 Patient's face showing thin beaked features, sparse dyed hair and corneal opacity in right eye.



Figure 4 The foot of the patient showing chronic ulceration over the malleolus.

only. The trunk was normal, but the extremities were slender (**Figure 1**). The scalp hair was white, sparse and receding. Facial hair along with the axillary and pubic hair were greyish white and sparse. There was microstomia and the nose was small and beaked. The skin of the face was atrophied, wrinkled with little subcutaneous tissue but was not sclerosed. Contractures of hands and feet with mottled hyperpigmentation were present with nail dystrophy (**Figure 2**). On examination of eyes, bilateral intraocular lens implants and corneal opacity in right eye were seen (**Figure 3**). Fifth molar tooth from the lower jaw was missing.

There was an eroded, hyperpigmented, crusted, punched out fixed ulcer about 3 cm over the lateral malleolus of the left leg (**Figure 4**). There were also crusted verrucous plaques over heels and atrophied skin on planter aspect of both feet.

Investigations showed a low hemoglobin (11g/dl). Liver and renal function tests, serum electrolytes and blood sugar showed no abnormality. Lipid profile was deranged with cholesterol 214mg/dl (reference value <200mg/dl), serum triglyceride 120mg/dl (reference value <150mg/dl), ALT 130IU/l (reference value 7-56IU/l), LDH 272 IU/l (reference value 100-250IU/l).

The HBsAg, anti-HCV antibodies and anti-HIV antibodies were nonreactive. In electrocardiogram sinus tachycardia with hyperacute T waves in V2, V3 leads was reported. X-ray of the left malleolus revealed osteomyelitic changes over the bone. Mobile vocal cords with patent airways were found on ENT examination. A skin biopsy from the ulcer revealed a nonspecific chronic inflammation with no malignant change.

Discussion

A large number of diseases manifest one or more features of apparent premature aging and most of the premature aging syndromes seem to be inherited with marked skin abnormalities.

WS is an autosomal recessive disorder that affects the connective tissue throughout the body. It is caused by null mutations at WRN locus, which codes for a member of RecQ family of DNA helicases.^{6-9,11} The disease is associated with excessive synthesis of collagen type I and III which is dependent on elevated messenger RNA(mRNA) levels.⁶ The locus of Werner Syndrome has been found on the short arm of chromosome 8 in both Japanese and non Japanese.^{5,7,11} Fibroblasts isolated from WS patients exhibit genomic instability, increased sensitivity to specific DNA damaging agents, slow proliferation, lengthened S-phase, and accelerated replicative senescence.^{5,7,16}

Much of the accelerated aging phenotype in Werner Syndrome is probably due to increased levels of the inflammatory cytokines produced by senescent cells. WS has been attributed to both increased cellular senescence and increased apoptosis.⁸ The sclerodermatous skin and blood vessel wall calcification contribute to the development of nonhealing ulcers and keratosis of the limbs.¹⁰

Originally this syndrome was described by Otto Werner in 1904.^{11,12,13} Clinical features described at that time were short stature, scleroderma-like skin alterations, cataract, premature aging of the face, grey hair and genital hypoplasia in 4 siblings. Oppenheimer and Kugel in 1934 reported the additional endocrinological abnormalities such as osteoporosis and hyperglycemia.¹¹

In 1945, Tannhauser described twelve symptoms: short stature, premature balding, poikiloderma, trophic leg ulcers, juvenile cataract, hypogonadism, amenorrhea, diabetes mellitus, blood vessel calcification, osteoporosis, metastatic calcification and tendency to occur in brothers and sisters.^{3,13} Between 1916 and 2002, 1300 cases were reported worldwide.

Individuals with this syndrome typically develop normally until they reach puberty. Following puberty they age rapidly and look many decades older.² The onset of WS might occur in individuals in their mid teens, or it may be delayed until an individual is as old as 30 years.⁶

Patients with WS have been reported to be at high risk for the development of malignant lesions.^{1,2,4,5,11,14} and malignancy is a frequent complication of WS.^{3,10} Defective homologous recombination is believed to be the primary reason for the chromosomal abnormalities and then genomic instability thus causing greatly increased risk of cancer, particularly sarcomas.^{1,8,13} Mesenchymal sarcomas are 10-times more common and other malignancies with elevated incidences are malignant melanoma, thyroid cancer, osteosarcoma and soft tissue sarcoma.^{3,4} However, in our case there was no evidence of malignancy but careful and periodic follow up of the patient may be required as malignancies can occur later on.

The clinical features include loss and greying of hair, impairment of normal growth, and loss of subcutaneous tissue and muscle mass in the extremities. The limbs become spindly with obese trunk. Atrophy of the skin and loss of subcutaneous fat result in a tense shining and adherent appearance of the skin mainly over the osseous prominences. Painful callosities may occur on the soles of the feet and indolent ulcers appear in the region of malleoli of the ankles, the Achilles tendons and heels and toes. Most patients show sparse hair in the regions of eyebrows, face, axillae and pubis. The facial appearance is usually changed as the taught skin of cheeks causing beaking of nose, shallow orbits and loss of periorbital connective tissue produce the appearance of proptosis, and artificial lenses are required after the extraction of rapidly progressing cataracts.¹⁴ The voice may become high pitched and hoarse with the peculiar thickening and vascularity of the vocal cords. Arteriosclerosis is strikingly premature and sexual underdevelopment result in sterility. Diabetes mellitus, osteoporosis and hypertrophic arthritis are common.^{1,7,8,13,14} However, no mental retardation is observed.⁶

The classical features of short stature, premature aging, atrophied sclerosed skin, eye lesions, microstomia, beaked nose, hypogonadism, spindly legs and a non healing ulcer over malleolus lead us to the diagnosis of WS. However, our patient did not show any cardiovascular involvement other than sinus tachycardia. Diabetes mellitus, osteoporosis, hoarseness of voice or any psychiatric abnormality could also not be detected.

The other causes of premature aging include progeria, acrogeria, Rothmund-Thomson syndrome and Cockayne syndrome. Progeria is a rare disorder with dwarfism and premature aging caused by mutations of lamin A (LMNA). The

major changes are in the skin, bone and cardiovascular tissues. Victims are characterized by large bald head with prominent veins, bird like facies and well proportioned little body. Acrogeria refers to the premature aging of the extremities without involvement of internal organs. The normal hair and eyes help to distinguish the condition from other progeroid syndromes. Rothmund-Thomson syndrome is hereditary and familial disease with clinical features of short stature, cataracts, pigmentation of skin, baldness abnormalities of bones, nails and teeth. Cockayne's syndrome may create confusion but pangeria is distinguished by loss and greying of hair, the lack of photosensitivity and ocular changes and the absence of disproportionately large extremities.^{1,3}

Average life expectancy for people with WS is to the mid-50s. Death usually occurs due to atherosclerosis, myocardial infarction or malignant tumors.^{1,2,4,6,7} WS is managed by treating symptoms, although there is no particular course of treatment for the condition itself.^{1,2,6}

Our patient was treated symptomatically specifically for foot ulcer and was advised regular follow up to detect any malignancy. He was also counseled about the prognosis and outcome of the disease. Early recognition of WS is important to assist identification of malignant tumours at an early stage in this patient group.

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