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Caricature of Ageing- A Case Report and Review of Literature of Werner Syndrome

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Werner's Syndrome (WS) also known as Pangeria is a rare premature aging autosomal recessive disorder. It affectes the connective tissue throughout the body with high prevalence in Sardinia and Japan.The signs of premature aging appears by second to third decade of life with increased risk of malignancies and atherosclerosis .The clinical features include characteristic aged appearance which typically begins to develop in their twenties which includes graying and loss of hair, a hoarse voice, scleroderma like skin changes. Patients have characteristic facial appearance described as "bird-like facies."

We present a case of a 43 year old male who was misdiagnosed and treated as a case of scleroderma previously. We have been motivated to report our case with Werner syndrome because he was very similar to scleroderma in terms of physical findings.

Keywords: Pangeria; caricature of ageing; premature; scleroderma; bird like facies.

ABBREVIATION

USG : Ultrasonography
ECG : Electrocardiography
ECHO : Echocardiography
ANA : Antinuclear Antibody
PM-SCL : Polymyositis Scleroderma

1. INTRODUCTION

Werner's Syndrome (WS) is a autosomal recessive hereditary disorder with highest

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incidence in Japan (1000 of 1300 cases reported worldwide) [1]. It is also known as pangeria or progeria adultorum .It has been described as "Caricature of ageing" by Epstein et al. In 1996 .It is a genomic instable disorder mainly affecting the connective tissue throughout body [1,2] . The patient is usually normal till puberty, thereafter there is accelerated premature aging which is characterized by short stature, senile appearance, early cataracts, joint contractures, early menopause and infertility, premature arteriosclerosis, scleroderma like features, premature canities, baldness, ulceration and increased risk of malignancy. It is caused due to mutation at the WRN locus which codes for DNA helicases, involved in replication and transcription process leading to excess synthesis of collagen type 1 and 3 [1,3].Death occurs in fourth to sixth decade due to cardiac abnormality or malignancy.

2. CASE REPORT

A 43 year male presented to our out patient department with complaints of tightening of skin over face and arms since 1 year. Further when probed he gave history of loss of hair all over body since 10 years, change in voice since 7 months . Patient surgerical history includes cataract surgery of left eye 5 years back and surgery for ruptured gastric ulcer 8 years back .The patient was born of a non consanguineous marriage and has no similar history in any of his other 2 siblings.For the above complaints the patient had consulted a dermatologist earlier who diagnosed it as a case of scleroderma on confirming it with skin biopsy.

On examination there was loss of hair over body, scalp, face (Fig. 1) salt and pepper pigmentation over bilateral shins (Fig. 2). Frontal bossing, inability to pinch skin over bilateral forearm and face, decreased mouth opening and beak like nose (Fig. 3) was present. The patient also had diffuse hyperpigmentation over body. A provisional diagnosis of scleroderma was considered on the basis of physical examination finding.

On further examination fundus revealed bilateral atypical retinitis pigmentosa with pseudophakia in the left eye. USG abdomen, ECG, ECHO and pulmonary function test were normal. Blood investigation revealed low haemoglobin, raised liver enzymes. Repeat skin biopsy showed sclerodermatous changes. ANA was borderline positive for PM-SCL. Genetic analysis was not carried out because of lack of facilities for the same. The patient was treated with vitamin supplements, hematinics and was advised for follow up, but was lost to follow up.

Absence of digital pits, Raynaud's phenomenon and ANA and RNA polymerase III positivity, normal pulmonary function test with characteristic prematurely aged appearance of face made us to arrive at a clinical diagnosis of WS.

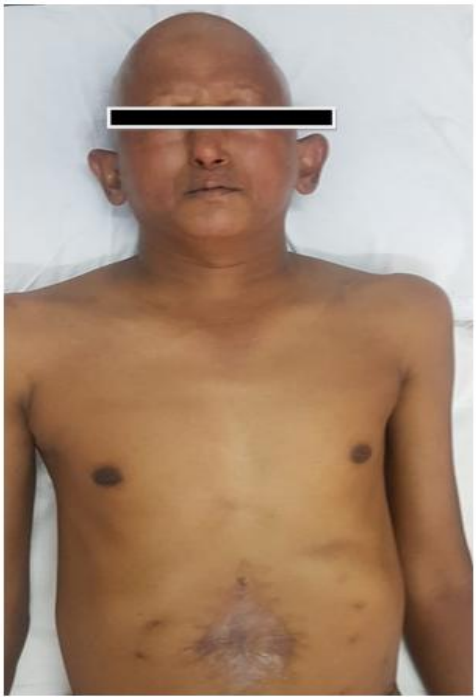

Fig. 1. Loss of hair over scalp and body with scar over

3. DISCUSSION

WS was initially described by Werner in 1904, when he reported four cases of brothers and sisters with symptoms and signs including juvenile cataract, pachyderma like alteration of the extremities, short stature, premature aging of the face, juvenile grey hair, and genital hypoplasia [3]. Oppenheimer and Kugel have additionally described endocrine abnormality like osteoporosis and type 2 diabetes mellitus in patient with WS [4].

WS is due to inheritance of an autosomal recessive gene with a gene frequency of 1- 5 per 1000 population [2]. It affects males and females in equal numbers. The disorder frequency has

been estimated at 1 to 20 per one million individuals in the Unites States. In the Japanese it is more common and is estimated to be 1 per 20,000 to 1 per 40, 000 [1]. The causal mutation has been identified in the Rec Q type DNA helicase gene (RECQL 2,) or the WRN gene which is located on the short arm of chromosome 8. It plays a significant role in DNA replication, repair, and telomere maintenance [1,2]. Due to the mutation there is abnormal metabolism of connective tissue, excessive synthesis of collagen I and III due to increased mRNA levels. 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 [5].

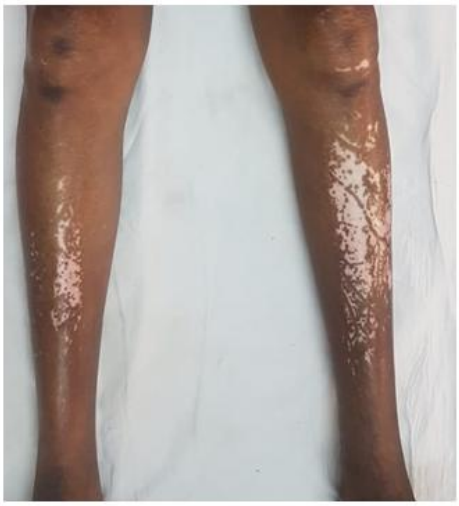

Fig. 2. Salt and pepper pigmentation on bilateral shins

The individual has normal growth till puberty, thereafter there is premature aging The clinical manifestation starts early at 14 to 18 years of age with greying of hair at the temples [1]. Skin changes are the earliest signs and more pronounced over the face and the extremities. It includes scleroderma-like skin changes, subcutaneous calcification and prematurely aged facies with beaked nose. The sclerodermatous skin changes and calcification of the blood vessels causes hyperkeratois of the limbs and pigment alteration thereby leading to development of recurrent non healing ulcer. There is a decrease in skin structure leading to an epidermal and dermal atrophy, reduction of the adipose tissue, decrease in sweat and sebaceous glands and reduction of hair follicles presenting clinically as sparse hair over eyebrows , face axillae and pubis [2].

The other clinical feature of WS include early onset of posterior or subcapsular type of cataract, premature arteriosclerosis leading cardiovascular complications , diabetes mellitus, short stature, slender limbs and hypogonadism leading to infertility [1,2,3]. The facial appearance is usually changed as the taut skin of cheeks causes beaking of nose and shallow orbits and additionally loss of periorbital connective tissue produce the appearance of proptosis [5]. The joints become fixed; with scelordactyly and acral gangrene. The voice may be high pitched and hoarse because of thickening of vocal cords [1].

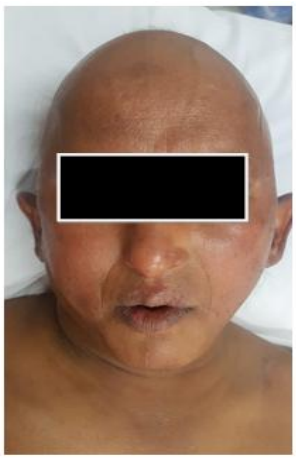

Fig. 3. Decrease mouth opening and beak like nose

The complications associated with WS are arteriosclerosis leading to cardiovascular death and malignancies. The most common malignancy seen in 10% of the patients with WS is fibrosarcoma. Other malignancies reported are osteosarcoma, leukemia, malignant soft tissue tumor, rhabdomyosarcoma, leiomyosarcoma, thyroid cancers, squamous cell carcinoma, basal cell carcinoma, malignant melanoma, breast carcinoma, and gastric carcinoma. Therefore, it is imperative to recognize WS at an early stage so as to facilitate the identification of subsequent malignant tumors [6]. The radiological changes show calcification of arteries, ligaments, tendons and subcutaneous tissue with osteoporosis of the legs [1]. Average life expectancy for people with WS is to the mid-50s. Death usually occurs due to atherosclerosis, myocardial infarction or malignant tumors [5].

The differential include other causes of premature aging syndrome like progeria, acrogeria, Rothmund-Thomson syndrome and Cockayne syndrome. Progeria is a rare disorder caused by mutations of lamin A (LMNA) mainly affecting the skin, bone and cardiovascular tissues. with dwarfism and premature aging. Paitents have large bald head with prominent veins, bird like facies and well proportioned little body. Acrogeria is a 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 is distinguished by the presence of photosensitivity and ocular changes and disproportionately large extremities [5].

Treatment for WS includes only symptomatic measures like ulcer management. Recently, Bosentan has been used in the management of ulcers [7,8]. Surgery is the option for treatment of ocular cataracts. Diabetes mellitus and hyperlipidemia, if present, should be adequately addressed. Results of various animal studies suggest that vitamin C supplementation could be beneficial for patients with Werner's syndrome [6].

4. CONCLUSION

The disease has to be recognized at an early stage in order to screen for any complications such as malignancies and cardiovascular complications. The management of these patient is multidisciplinary for the treatment and prevention of complications.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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