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WERNER SYNDROME: A NEW CASE REPORT

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Abstract
"Werner's syndrome" or premature aging syndrome is a rare autosomal recessive genetic disease. It is responsible of several complications related to age, including atherosclerosis and association with cancer. We report the case of a 36 year-old-patient, admitted to department of Internal Medicine of the military hospital of Tunis for suspicion of systemic sclerosis. The patient had all the major signs of Werner syndrome (bilateral cataract, sclerotic skin, "bird face", baldness, small size, parental consanguinity) and 4 minor signs (type 2 diabetes, hypogonadism, squeaky voice, and flat feet). She has also a brother with the same morphotype died at the age of 32 by a myocardial infarction. The current follow-up time is 9 years.

Key words: Werner syndrome; adult progeria; malignancy

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Introduction

Werner's syndrome (WS) is a disease causing premature aging. Its clinical manifestations include several signs usually associated with age, such as prematurely gray hair, alopecia, cataract, atherosclerosis, arteriosclerosis, osteoporosis, and a high incidence of some types of cancer [1]. Werner's syndrome is typically transmitted as an autosomal recessive disease, but atypical forms such as autosomal dominant transmission have also been reported. The prognosis depends on the associated diseases: atherosclerosis with its cardiovascular and neurological complications, insulin-resistance and cancer risk. The treatment is still limited to a multidisciplinary management of the diseases that complicate this syndrome [1,2]. In this regard, we report a case of a 36-year-old patient, followed for WS in the department of internal medicine at the military hospital of Tunis.

Case Report

Mrs. NN 36 years old, unmarried, born to consanguineous parents, was admitted to our department for suspicion of systemic sclerosis. Physical examination revealed a total alopecia, depletion of pilosity with signs of hypogonadism, sharp nose, facial skin was tough and tight with some telangiectasia (Fig. 1a, b). Members were slender with obvious atrophy (Fig. 2), her feet were flat with plantar hyperkeratosis (Fig. 3) and she had hyperchromic spots at the trunk and limbs. Moreover, we noted an increase in the volume of the left lobe of the thyroid containing a firm and painless nodule. She weighed 38 kg for a height of 1.50m (BMI = 16.8). She had secondary amenorrhea since the age of 28 and complained from a decline in visual acuity and a changement in her voice that gets squeaky for few months.

Laboratory tests showed hyperglycemia (Fasting glycemia=2.30 g/l) with a high level of glycated hemoglobin (HBA1C=12.9%) and hypertriglyceridemia (TG=3.12 mmol/l). The immunological tests were negative (antinuclear antibodies<0, anti Scl70<0, rheumatoid factor<0, anti-neutrophil cytoplasmic antibodies<0) and complement components C3, C4 and CH50 were normal. Free T4 and Thyroxin Stimulating Hormone have normal rate. Tumor markers' levels (CEA, CA 19-9 and CA-125) were not high. Follicule Stimulating Hormone and Luteining Hormone levels were above 40mU/l suggesting an early menopause. Ophthalmologic examination revealed a bilateral nuclear cataract. Cervical ultrasound showed a large heterogeneous left thyroid nodule with a central and peripheral vascularisation. Pelvic ultrasound showed atrophic ovaries.

The diagnosis of Werner syndrome was strongly suspected seen the particular signs in our patient especially the skin lesions, signs that are usually present in elderly patients, in addition to parental consanguinity as her brother died with the same symptoms prematurely at the age of 32 by a myocardial infarction. In our case, the course was complicated with type 2 diabetes requiring insulin after the failure of antidiabetic drugs combining. The patient underwent a left loboisthmectomy and pathological anatomy of the nodule concluded that it was a micro and macro-vesicular adenoma with no signs of malignancy.

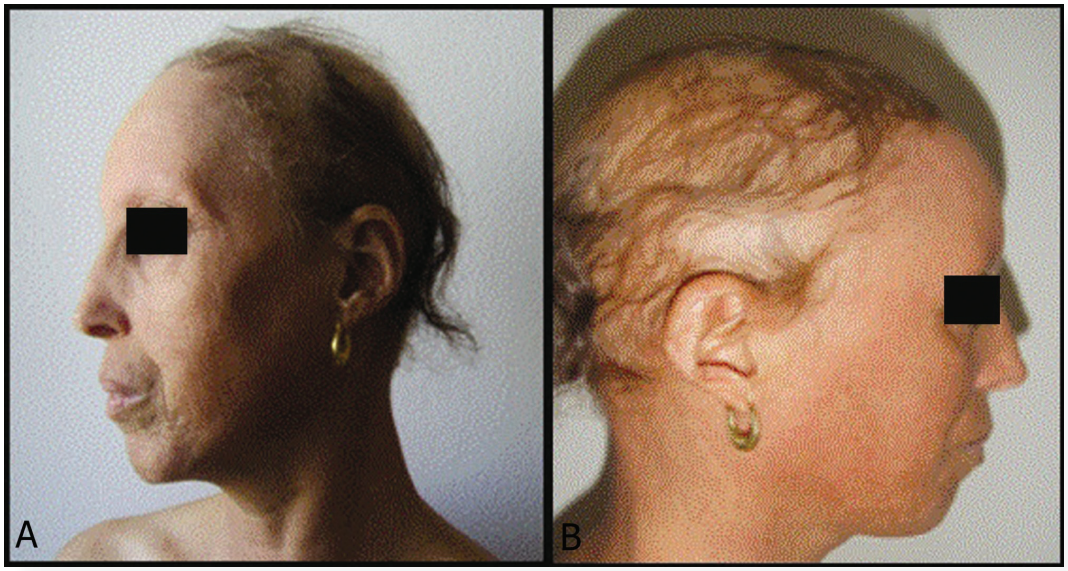

Figure 1a. Sharp nose, tough and tight facial skin with some telangiectasia; 1b. Total alopecia.

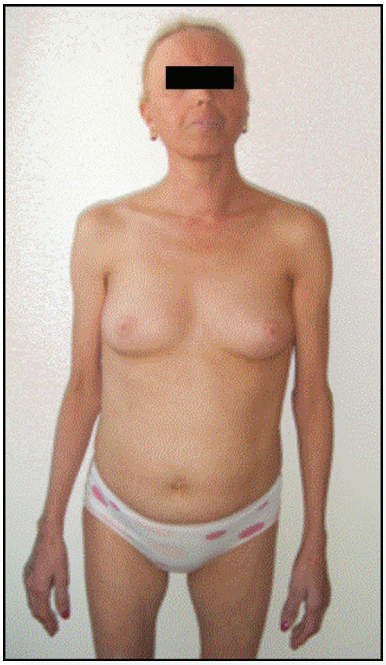
Figure 2. Slender members with obvious atrophy, depletion of pilosity with signs of hypogonadism.

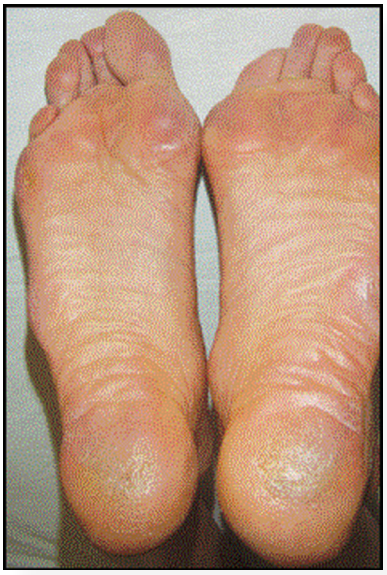
Figure 3. Flat feet with plantar hyperkeratosis.

Discussion

Werner's syndrome (WS) was discovered by Werner in 1904. The diagnosis criteria proposed in 1994 include major signs combining: bilateral cataract, skin changes (thin skin, skin atrophy, pigmentary abnormalities, cutaneous ulcers, hyperkeratosis, subcutaneous atrophy), a characteristic facial appearance "bird face" (tapered nose, decreased subcutaneous tissue), short stature, premature graying of hair or early baldness, parental consanguinity or a first cousin reached by the disease [1]. Minor signs of WS are: type 2 diabetes, hypogonadism (delayed development of secondary sexual characteristics, hypofertility, testicular or ovarian atrophy), osteoporosis, osteosclerosis of distal phalanges of fingers or toe [2], premature atherosclerosis which can cause myocardial infarction, mesenchymal tumors (sarcomas) and unusual sites of melanoma and osteosarcoma. Common carcinomas are also observed [3,4]. Abnormal voice (squeaky, acute) and flat feet are also minor signs of WS [5].

In our patient, the diagnosis of WS was retained seen the presence of all the major signs (bilateral cataract, sclerosis of the skin, "bird face", bald, small size, parental consanguinity) and 4 minor signs (type 2 diabetes, hypogonadism, squeaky voice, flat feet**).**

Werner's syndrome is a genetic disorder transmitted in an autosomal recessive way, its prevalence varies with the rate of inter-marriage in populations. In the Japanese population it is 1/20,000 to 1/40,000 [6]. In the U.S. population prevalence is estimated at 1/20,000.

The percentage of consanguineous marriages in Tunisia is around 30%, raising the prevalence of Werner syndrome which is not known. The pathogenesis of SW has been well studied, a mutation of WRN gene is the only known responsible of Werner Syndrome. This mutation is present in 90% of affected individuals, revealed via a genetic molecular test. It is responsible for the loss of function of the WRN protein leading to early senescence [7].

The severity of the WS is due to its several complications dominated by atherosclerosis. Patients may develop different forms of atherosclerosis, specially that affecting the coronary arteries and leading to myocardial infarction that is the first cause of death in WS, such as the case of our patient's brother. Cancers also threaten patients with Werner syndrome. Our patient had a thyroid nodule which pathological anatomy eliminated thyroid carcinoma. Skin complications are also reported. Giuseppe F. et al [8] published a case of Werner syndrome in a patient whose quality of life was highly affected and in which the main complaint was a painful leg ulcer, relapsing for 9 years.

Prevention of secondary complications through a healthy lifestyle aim to reduce the risk of atherosclerosis: smoking cessation, regular physical activity, weight control. The eviction of trauma, skin care and regular checkups are necessary in the follow-up. WS patients must be monitored with a glucose balance, lipidic profile, and annual eye exam. Monthly monitoring of cutaneous manifestations and regular cancer screening is needed. The mean age of death in WS is about 54 years [9]. In our patient, the current follow-up time is 9 years , the course was complicated with type 2 diabetes and we have no malignancy detected.

Conclusion

In conclusion, the case is presented for the rarity of the syndrome, which should be kept in mind to avoid misdiagnosis, allow preventive measures, and promote adequate periodic screening for dermatological, ophthalmic and cardiovascular complications associated with premature aging, especially malignancies.

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