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Leg ulcer in Werner syndrome (adult progeria): A case report

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Abstract

Werner syndrome (WS; MIM#277700) or adult progeria, is a rare disease, associated with mutations of a single gene (RECQL2 or WRN), located on chromosome 8 (8p12). It codes a DNA-helicase, whose defects cause genomic instability. The highest incidences are reported in Japan and Sardinia (Italy). On this major island of the Mediterranean Basin, the WS cases have been observed in the northern areas. The authors describe the apparently first case reported in southern Sardinia, a 51-year-old woman, who was born in and resides in the province of Cagliari. She presented with a 9-year history of an intractable leg ulcer and other characteristic symptoms, including “bird-like” face, high-pitched voice, premature greying, short stature, abdominal obesity in contrast with thin body type, scleroderma-like legs, decreased muscle mass, diabetes, atherosclerosis, and premature menopause. A specialized genetic Institute of Research (IRCCS-IDI, Rome) confirmed the clinical diagnosis. There is no cure or specific treatment and patients must be periodically screened for an increased risk of cardiovascular and cerebrovascular disease and malignancies. Among the many findings, leg ulcers significantly affect the patient’s quality of life. This problem may send the patient to the dermatologist, who finally suspects the diagnosis. Poor response to medical treatment may require aggressive repeated surgery, with poor or temporary results.

Introduction

Werner syndrome (WS; MIM#277700), or adult onset progeria, firstly described in 1904 by Otto Werner in his graduation thesis at the University of Kiel [1], is a rare autosomal recessive or sporadic disease [2, 3, 4], related to mutations or deletions in a single gene, located on human chromosome 8p12. This encodes a homolog of the *Escherichia coli* RecQ DNA helicase, therefore named RECQL2 or WRN gene. Although the exact role of the defective protein has not been clarified, premature aging describes the many clinical features of the syndrome; several studies on the molecular aspects have demonstrated defects in DNA replication, repair, and transcription in the WS cells, resulting in genomic instability [5]. The disease is classified under the medical heading of the “Progeroid syndromes,” and usually is noticed after adolescence, when the body begins to age faster than normal. By the 4th or 5th decade of life, the patient seems much older than the chronological age. It is considered a model for the study of human aging [6] and a physiological loss of function in the same gene has been postulated in normal senescence. In addition, some distinctive features are not typically associated with aging, such as facial dimorphism, hypogonadism, and sclerodermoid changes of the soft tissues, which significantly affect the patient’s quality of life.

The original observation by Werner regarded two brothers and two sisters aged between 31 and 40, who showed visible signs of aging. They exhibited short stature, baldness, greying hair, bilateral juvenile cataract, pseudosclerodermic skin, genital hypoplasia, and leg ulcers. Only in 1934, Oppenheimer and Kugel suggested the autonomy of the disease from the Rothmund-Thomson syndrome including other systemic symptoms such as diabetes, hypogonadism, and osteoporosis and proposed the name WS [7]. Subsequently, in 1945 Thannhauser codified the disease in details [8], listing a comprehensive series of clinical and laboratory findings: consanguinity, bird-like facial appearance, raspy and high pitched voice, decreased muscle mass, short stature and spindly limbs, precocious greying and hair loss, scleroderma and poikiloderma, potential predisposition to diabetes, skin ulcers, bilateral juvenile cataract, hypogonadism,

osteoporosis, hardening of soft skin tissue, and premature atherosclerosis. The average life span is 47 years and death is usually related to the increased risk of cardiovascular and cerebrovascular accidents, as well as malignant tumor development [5, 6, 9].

Epidemiological studies confirmed the rarity of the disease, affecting both sexes, with an overall incidence of 1 in 1 million births. About 1300 cases have been cited in the medical literature [5, 9] and the highest incidence is documented in Japan, ranging from one case per 300,000 inhabitants to 1 in 3500 births in some communities with high consanguinity rates (70%) [9, 10, 11]. In Italy, the majority of cases are born in the northern areas of Sardinia, a major island of the Mediterranean Sea, where the estimated incidence is of 1 case in every 59,000 inhabitants [12, 13]. This high frequency is certainly related to geographical isolation and the large number of marriages within related family groups [13]. On the other hand, the disease seems not to be so frequent in southern Sardinia; a review of the literature did not document reports in patients born and resident in this geographical area, including the capitol city Cagliari.

Clinical case study

A 51-year-old female, who was born and is a resident of a little city of the province of Cagliari in the south of Sardinia, whose ancestors originally came from the same city, presented to the local dermatology clinic with a skin ulcer located in the flexor region of her left leg, at the lower third. Our team examined the ulcer fist only in September 2006, although the patient complained about its presence since 2002. Her ulcer first had been treated with medical dressings from different surgeons and vascular specialists, with temporary benefits and relapses. The family medical history was negative for consanguinity and her only sibling, a man of 45, was in a good state of health. The past personal history revealed type II diabetes mellitus, first diagnosed in 2000 and treated with oral antidiabetics, acquired hypothyroidism, osteoporosis, hypertension, dismetabolic hepatopathy, and precocious menopause.

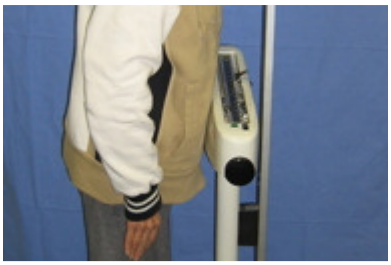

Figure 1

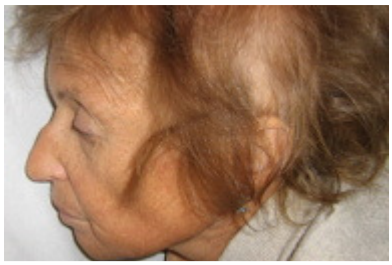

Figure 2

The patient gave her consent to take and publish some pictures illustrating her characteristic face, habitus, and ulcer features. On physical examination, the patient presented short stature (156 cm), 40 kg of weight (Figure 1), hoarse voice, and a peculiar face (Figure 2): thin with a pinched expression, prominent eyes, pointed chin, beaked nose, taut lips, prominent teeth, and micrognathia. Her hair was diffusely thin and grey; the skin presented extensive signs of xerosis and notable subcutaneous atrophy. Her legs were spindly, without subcutaneous fat and reduced muscule mass. On the distal third of the right leg (Figure 3) there was an irregularly oval shaped ulcer of about 8 cm in diameter, with dry base and shallow depth, with little granulation tissue. It was covered with necrotic and sero-fibrinous debris and the borders were erythematous, swollen, and sloping. The surrounding skin was hairless, dry and shiny, firm, and woody at palpation. The lesion was painful while standing or walking. Considering the presence of cardinal signs of Werner Syndrome (skin changes, short stature, graying hair, and cataracts), plus additional pathologic conditions, the Werner Syndrome was suspected and DNA testing (Sequence analysis of WRN coding region) was sent to a specialized genetic Institute of Research (IRCCS-IDI, Rome), which after several weeks confirmed the clinical diagnosis.

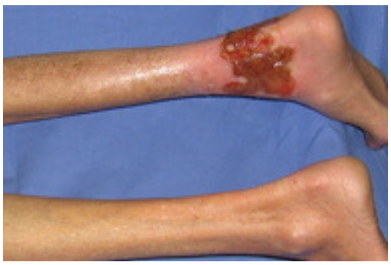

Figure 3

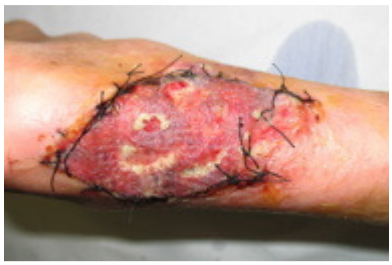

Figure 4

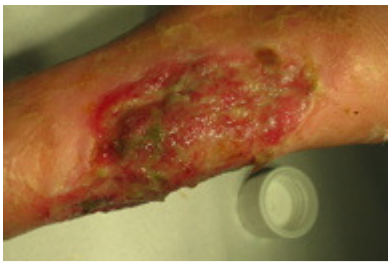

Figure 5

Laboratory investigations showed a slight hypochromic anemia (RBC 3-98 x 10/microL; Hb 10.6 g/dL), a high erythrocyte sedimentation rate (76 I h), a moderate increase in basal glycemia (156 mg/dl) and GammaGT (82 UI/l). A culture test from the ulcer base was positive for *Pseudomonas aeruginosa* growth. A biopsy of the base and edge of the ulcer allowed us to exclude any type of skin cancer. An X-ray of the leg, the tibio-tarsic joint, and the foot confirmed extensive uneven (worm-eaten) osteoporosis, with widespread soft tissue calcification. An examination of the lower limb blood vessels, using an ecocolor doppler, showed moderate atherosclerosis but with no serious compromising of the blood flow. The patient was treated with suitable antibiotics and medicated with silver enriched hydrocolloids until the repeated culture tests were negative. A Thiersch skin graft was taken from the side of the thigh and placed on the raw wound (Figure 4). Though initially successful with almost complete ulcer re-epithelialization, the ulcer relapsed after a period of two months (Figure 5).

Discussion

WS is a rare cause of skin ulcerations, although the ulcers are present in 50 percent of these patients [14, 15] and generally are the main cutaneous symptom of presentation. This may lead to the diagnosis of the disease, as in the case of our patient. Werner sporadic forms might elude medical suspicion until adult age, if the general condition of the patient is good. Our patient did ignore her condition and was not aware of the increased risk of cardio-cerebro-vascular disease or malignancies. From an epidemiologic point of view, the case is important because it is the first observed in decades in the main dermatology clinic of the Province of Cagliari, capitol city of Sardinia. This clinic serves a vast population in the southern part of the island, accounting for about 460,000 inhabitants. The northern areas of the same island house a well-documented cluster of WS, with an incidence of 1:59,000 inhabitants [13]. Different historical conditions have characterized the Sardinian provinces over the centuries. The southern areas have been more prone to invasion and colonization and less prone to consanguineous marriage. On the other hand, the southern population is more favored to travel and more connected with the Italian mainland. The observed sporadic case might therefore conform the worldwide incidence of the disease in the general population. The diagnosis of the syndrome is usually clinical, but the disease progression is slow, beginning after adolescence. Typically the patient, as well as the general practitioner, may undervalue the signs and symptoms until the 4th or 5th decade of life, when the patient seems much older than the chronological age. The dermatologist is often the first physician pursuing the diagnosis because of the facial dimorphism, the premature hair greying and baldness, with exaggerated wrinkling on the face, the decreased muscle mass, and thickening of the skin with loss of fat. Then, the high-pitched voice and the coexistence of systemic symptoms complete the picture. At examination, our patient was already affected by diabetes mellitus, bilateral cataracts, hypogonadism, diffuse atherosclerosis, severe osteoporosis, and premature menopause. Careful screening for malignancies was negative and the main complaint was concerning the painful leg ulcer, relapsing for 9 years. The pathogenesis of ulcers seems to be connected to a series of factors including xerosis, subcutaneous atrophy, insufficient arterial perfusion resulting from atherosclerosis, diabetes, a distortion/alteration in the normal structure of the foot, and most notably, anomalous fibroblastic activity [11, 16, 17, 18]. Various studies support that WS patients manifest a series of progressive DNA mutations with reduced regenerative capacity of fibroblasts and diminished proliferation in vitro, after stimulation with recombinant platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) [18, 19]. WS ulcers generally affect the lower limbs (in the malleolar and Achilles heel area) or less frequently, the

cubital region [4, 10, 15]. A biopsy should be performed to exclude a neoplastic ulcer; the development of a squamous or basal cell carcinoma is not uncommon in this chronic pathology [20, 21]. Treatment is almost always problematic for various reasons such as susceptibility to bacterial over-infection/multiple bacterial infections, the lack of an adequate vascular supply, and the loss of subcutaneous tissue resulting in frequent exposure of tendons.

Surgical techniques like rotation flaps have been applied with success in some cases [22, 23], but certain areas such as the ankle and foot do not have adequate perfusion and supportive subcutaneous tissue to allow flap viability. For this reason, we tried a Thiersch graft, using the postero-lateral aspect of the thigh as donor to cover the ulcer, once the *Pseudomonas aeruginosa* over-infection was cleared. Unfortunately, WS affects granulation tissue production and maintains an unhealthy state that hampers proper grafting. Although initially effective, recurrence of the ulcer occurred. Other choices, such as direct application of growth factors on the ulcer base to favor granulation, especially the platelet derived growth factor (PDGF-B) [24], may be attempted. In addition, hyperbaric therapy and the use of allograft and artificial skin grafts composed of bovine collagen with glycosaminoglycans and silicon are anecdotal and the results on long term follow-up are not reported.

In conclusion, the case is presented for the rarity of the syndrome, which should be kept in mind to avoid misdiagnosis, provide genetic counseling, allow preventive measures, and promote adequate periodic screening for complications, especially malignancies. Our patient's quality of life is highly affected by the ulcer development and treatment implementation is crucial. A revision of current literature did not report data on the mean age of leg ulcer appearance, but Japanese papers report two siblings, aged 26 and 28 years, and one other patient, aged 37. An Iranian case was a 46-year-old [10, 14, 25]. Our patient was a 41-year-old when she started suffering from leg ulcers. Therefore, it seems that leg ulcers affect young adults during the working life age.

Several problems hamper healing in WS patients: malfunctioning of fibroblastic activity, insufficient subcutaneous tissue, co-existing pathologies such as diabetes and atherosclerosis, chronic anemia, and predisposition to infections.

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