CASE REPORT

Werner's syndrome: incidental finding during pregnancy

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SUMMARY

Werner's syndrome (WS) is a rare autosomal recessive disorder, characterised by skin changes prematurely during adolescence. An unusual case of WS was found in a 27-year-old pregnant woman who presented to the hospital with a history of uncontrolled hypertension at 32 weeks of gestation. All clinical features corresponding to WS (early aging of skin, hair loss, blurred vision and diabetes type 2) appeared to match with the prospective diagnosis, which was confirmed later with genetic testing. The pregnancy became complicated due to oligohydramnios and therefore a caesarean section was carried out in order to preserve the fetus. Despite all implemented efforts, the patient died intraoperative as a result of cardiac arrest and its complications. Successfully, the newborn survived and it was further investigated to exclude this condition.

our clinical suspicion towards this condition; an echocardiography was performed subsequently supporting these premature senescence findings attributable to arteriosclerotic changes in vessels.¹

CASE PRESENTATION

A 27-year-old woman of indigenous ethnic, without any family history of genetic disorders, was admitted to the hospital due to uncontrolled hypertension at 32 weeks of gestation. She described that since 13 years of age, she started with wrinkling of skin, generalised hyperpigmentation, cloudy vision and hair discolouration accompanied by its loss. During history taking, she mentioned having been diagnosed and treated for diabetes mellitus type 2 for 4 years. Her diabetes was being controlled with metformin 850 mg twice daily, however, the patient did not have any antenatal control. At this time, she presented to the hospital mentioning that was coursing its first pregnancy.

Physical examination revealed a short stature woman, with thin upper limbs and slender trunk with scarce fat tissue distribution, bird-like face with aquiline nose and sunken eyes. Her voice was tinny and highpitched, blood pressure 210/110 mm Hg, weight 43 kg and height 145 cm.

Overall skin inspection showed scleroderma-like skin changes, with hyperkeratosis without desquamation, thin brown hair (dyed) and opacities in both eyes (cataracts); funduscopy was not possible to be conducted. Her thorax was flat with absence of axillary hair and hypotrophy of mammary glands, and she presented nail atrophy of hands and feet (figures 1–4).

On auscultation, a harsh systolic murmur was noticed concomitant to 'Gallavardin phenomenon'; her abdomen was protruding with a fetus in its

BACKGROUND

The case represents a rare pathology, which in combination with pregnancy is yet more intricate. Actually, the literature describes only a few reported cases of this syndrome in association with pregnancy around the globe. This case contributes to casuistry of the region of Central America, where no cases have been reported previously¹ and thereby it emphasises the importance of identifying significant clinical features of this syndrome in the absence of immediate genetic investigations. Clinically, this patient meets Goto's criteria for Werner's syndrome (WS)^{2–4} (table 1).

Owing to hypogonadism pregnancy manifests infrequently in patients with WS, while obstetric complications arising from WS are frequent, although its association remains unidentified.⁵ Certainly, this patient also presented signs of aortic stenosis which added further elements to maintain

Table 1 Major self-assembly body systems in Werner's syndrome

Self-assembly body system	Mediators inside and between systems	Symptoms
Connective tissue	Adhesion molecules (glycosaminoglycans, fibronectin, collagens) cytokines	Fibrosis, cataract, skin sclerosis, osteoporosis, grey hair, arthropathy
Immune	Hormones (thyroxine, insulin, sex hormones) metabolites	Diabetes, hypogonadismo, Grave's disease hyperlipidaemia, gout
Endocrine-metabolic	Cytokines, NK cells autoantibodies	SLE, Sjorgren's, Graves' diseases
Nervous-psychological	Neuropeptides? Cytokines	Brain atrophy, schizophrenia
Mixed		Migaligancy, atherosclerosis
Mediators which may affect the deterioration process are indicated. Typical symptoms in the respective body systems are also shown. SLE, systemic lupus erythematosus

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Figure 1 Scleroderma-like skin changes, with hyperkeratosis without desquamation, thin brown hair (died); her thorax was flat with absence of axillary hair and hypotrophy of mammary glands.

cavity of approximately 28 weeks, measured by uterine height. No masses were found during palpation of the abdomen; bowel sounds were present.

Lower limbs did not reveal any signs of ulceration or telangiectasia.

INVESTIGATIONS

Pathology results for haematology, serum creatinine, electrolytes and autoimmune investigations were within normal ranges. Other investigations showed glucose 126 mg/dL and glycosylated hemoglobin 8.3%; urinalysis was negative for proteins.

Transthoracic echocardiography reported a severe calcification of the aortic valve with a mean gradient value of 46 mm Hg, accompanied by systolic dysfunction and an ejection fraction of 45%, the valvular area corresponded to 0.7 cm².

Obstetric ultrasound showed signs of oligohydramnios and the presence of intrauterine growth restriction.

DIFFERENTIAL DIAGNOSIS

- ▶ Mixed connective tissue disease
- ▶ Systemic sclerosis
- ▶ Rothmund-Thomson syndrome
- ▶ Hutchinson-Gilford syndrome

Figure 2 Abdomen was protruding with a fetus in its cavity of approximately 28 weeks measured by uterine height.

Figure 3 Scleroderma-like skin changes of both hands.

TREATMENT

The patient did not receive any previous treatment, neither antenatal control. At this stage, we only knew by medical history that she was being treated for diabetes mellitus type 2 at her local health community centre. Although, if the condition had been detected previously, treatment may have been established. We were unaware of the patient's condition until admission to the hospital.

OUTCOME AND FOLLOW-UP

During fetal monitoring in the intensive care unit, fetal distress signs started to appear, whereby caesarean section delivery was decided. The patient suffered from cardiac arrest and its complications, and died intraoperative 5 days after her admission. Genetic tests were immediately taken from the patient and the newborn and sent for analysis in a specialised centre. LMNA tested negative for the mother and sequence analysis of WRN coding region confirmed her clinical diagnosis; the LMNA and WRN genes were not found altered in the newborn.

The patient's family financed all genetic testing.

DISCUSSION

WS has been designated as an autosomal recessive disorder involving the helicase gene on chromosome 8, described by skin and hair changes, glucose intolerance, osteoporosis, cataracts and hypogonadism usually in the second or third decade of

Figure 4 Scleroderma-like skin changes, of both feet with hyperkeratosis without desquamation.

life.⁶ It could be challenging to make a diagnosis of WS and differentiate it among other sclerodermiform-related pathologies; however the association of these clinical findings, accompanied by the appearance of early metabolic diseases, could lead to an assertive outcome. Occasionally, these changes might not be present in the early stages.⁷ The patient was being treated by diabetes type 2, which provided a key element to our clinical scenario.

The International Registry of Werner syndrome has developed a list of cardinal signs and symptoms that may be used to diagnose WS. The cardinal signs and symptoms, based on an onset after 10 years of age, include bilateral cataracts, characteristic skin, 'bird like' faces (ie, a pinched nasal bridge and loss of subcutaneous tissue), short stature, premature greying and/or thinning of scalp hair, consanguinity and positive 24 h urinary hyaluronic acid test.⁸

The secondary symptoms that have been described are diabetes mellitus type 2, hypogonadism, osteoporosis, evidence of osteosclerosis of the distal phalanges or toes, soft tissue calcification, atherosclerosis, neoplasms, flat feet and abnormally high-pitched voice.⁸⁻⁹

The definitive diagnosis is considered when all cardinal symptoms are present and also two secondary signs are identified. A probable diagnosis is considered when three cardinal signs are present, and two secondary signs are identified. Finally, a possible diagnosis is that in which cataracts or dermatological disorders are present and one of four secondary symptoms are identified.¹⁰

Another method for diagnosing WS was established in 1997. This proposed method is defined as one in which four of the five following symptoms are identified: consanguinity, characteristic facial appearance, premature senescence, scleroderma-like skin changes and endocrine/metabolic disorders.¹⁰ Despite the fact that these phenotype-based standards have been set, it is important to use diagnostic and genetic testing in order to diagnose WS.

This progeria is caused by mutations at the WRN gene encoding the helicase DNA, and is also linked with excessive production of collagen types I and III which results in accelerated aging of the body.¹¹⁻¹³ In this instance, the patient presented incongruity between her biological age and her appearance, which could be a unique feature for WS.¹ Usually this is an adult-onset condition, with the absence of a growth spurt during puberty as the earliest sign.¹³ Similarly, the physical characteristics such as body habit, early aging signs, hypogonadism and scleroderma-like changes, are cardinal signs that cannot be disregarded as part of this disorder.²⁻¹³

The deterioration of the endocrine system in WS is reflected through hypogonadism from early ages; in spite of this, the patient was able to get pregnant. Torbé *et al*¹⁴ described the possibilities of pregnancy in patients with WS as infrequent. In the interim, Ogawa *et al*⁵ described hypertension and intra-uterine growth retardation as obstetric complications described from patients experiencing this disorder. Such problems were exhibited by the patient since she presented to the hospital. Owing to fetal distress while monitoring, a caesarean section was decided promptly in order to prevent complications during delivery.

As a result of her aortic stenosis and severe calcification of vessels, the patient died, in the operating theater. This phenomenon could be explained by the excess of collagen produced by fibroblasts that alters the extracellular matrix composition, predisposing patients with WS to a premature atherosclerotic state.¹⁵ Goto *et al*¹ had attributed atherosclerosis as a sort of 'silent auto inflammation' in patients with this disorder.

In this case, diabetes mellitus was not appropriately managed and meticulously investigated. By the time that the patient presented to the hospital, pregnancy was already complicated; otherwise, treatment could have been promising. Currently treatment for aortic stenosis during pregnancy has been reserved to severe cases, where percutaneous balloon aortic valvotomy can be attempted, although risky.¹⁶

On the other hand, diabetes also could have been handled as a pre-existing condition, including insulin as a main therapy and close monitoring of glycaemic controls. A structured multidisciplinary approach to avoid metabolic complications could have also been included.¹⁷⁻²⁰

Learning points

- ▶ Alternative clinical methods could be used to diagnose Werner's syndrome (WS), in the absence of direct genetic testing.
- ▶ WS might be suspected by incorporating hallmark clinical signs and associating them with metabolic conditions, instead of suspecting isolated pathologies.
- ▶ Owing to the nature of WS, this ought to be managed in a multidisciplinary approach, especially during pregnancy; obstetric vigilance should be encouraged in order to prevent and diminish death and potential risks, inherent both in the disorder and the gestational period.

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