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ORIGINAL

Diabetes mellitus coexisted with progeria: a case report of atypical Werner syndrome with novel LMNA mutations and literature review

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Abstract. Werner syndrome (WS) is a rare, adult-onset progeroid syndrome. Classic WS is caused by *WRN* mutation and partial atypical WS (AWS) is caused by *LMNA* mutation. A 19-year-old female patient with irregular menstruation and hyperglycemia was admitted. Physical examination revealed characteristic faces of progeria, graying and thinning of the hair scalp, thinner and atrophic skin over the hands and feet, as well as lipoatrophy of the extremities, undeveloped breasts at Tanner stage 3, and short stature. The patient also suffered from severe insulin-resistant diabetes mellitus, hyperlipidemia, fatty liver, and polycystic ovarian morphology. Possible WS was considered and both *WRN* and *LMNA* genes were analyzed. A novel missense mutation p.L140Q (c.419T>A) in the *LMNA* gene was identified and confirmed the diagnosis of AWS. Her father was a carrier of the same mutation. We carried out therapy for lowering blood glucose and lipid and improving insulin resistance, *et al.* The fasting glucose, postprandial glucose and triglyceride level was improved after treatment for 9 days. Literature review of AWS was performed to identify characteristics of the disease. Diabetes mellitus is one of the clinical manifestations of WS and attention must give to the differential diagnosis. Gene analysis is critical in the diagnosis of WS. According to the literature, classic and atypical WS differ in incidence, pathogenic gene, and clinical manifestations. Characteristic dermatological pathology may be significantly more important for the initial identification of AWS. Early detection, appropriate treatments, and regular follow-up may improve prognosis and survival of WS patients.

Key words: Diabetes mellitus, Progeria, Werner syndrome, *LMNA* gene, Lipoatrophy

WERNER SYNDROME (WS), also known as adult progeroid syndrome, is a rare, early-onset, and age-related disease characterized by segments of aging phenotypes [1]. The prevalence of WS was roughly estimated to be 1:100,000 in Japan and 1:1,000,000–1:10,000,000 outside of Japan [2]. Classic WS (CWS) is an autosomal recessive disease caused by mutations of the *WRN* gene, which encodes a member of the RecQ family of DNA helicase. WS cases without *WRN* mutations are usually categorized as "atypical WS" (AWS) [3]. As in 2014, the International Registry of Werner Syndrome has recruited 202 molecularly confirmed cases of WS, 142 (70%) patients exhibited *WRN* mutations, 11 (5%) patients exhibited *LMNA* (encoding nuclear lamin A/C) mutations, and 49 (24%) patients exhibited neither *WRN* nor *LMNA* mutations [3]. WS patients are born normally, with normal growth, development, and cognitive function in childhood. The first clinical sign is lack of pubertal growth spurt during the teen years. The patients die prematurely during the fourth or fifth decade of life [4, 5]. Diagnostic criteria for diagnosis of WS based on phenotype presentation was established by the International Registry of Werner Syndrome (www.wernersyndrome.org). Cardinal (cataracts, dermatological pathology and characteristic facies, short stature, parental consanguinity or affected sibling, premature greying and/or thinning of scalp hair) and further signs and symptoms (diabetes mellitus, hypogonadism, osteoporosis, osteosclerosis of distal phalanges of fingers and/or toes, soft tissue calcification, evidence of premature atherosclerosis, neoplasms, voice change, flat feet) are used to make a "definite" (all the cardinal signs and two further signs), "probable" (the first three cardinal signs and any two others), and "possible" (either cataracts or dermatological alterations and any four others)

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diagnosis of WS [6]. Confirmation of a clinical diagnosis requires additional genetic testing according to another Japanese-related set of diagnostic criteria [7].

Based on the diagnostic criteria of WS [6], a young Chinese woman with insulin-resistant diabetes mellitus (DM), irregular menstruation, and progeria was diagnosed with "possible" WS. Genetic sequencing of the *WRN* and *LMNA* genes was conducted and a pathogenic mutation p.L140Q in exon 2 of *LMNA* gene was identified. In addition, genetic sequencing of the *LMNA* gene for her parents identified the same pathogenic p.Ll40Q mutation in the *LMNA* gene in her father.

Patients and Methods

A 19-year-old native Chinese woman presented to the Department of Endocrinology and Metabolism with a chief complain of irregular menstruation for nearly 2 years. She attained menarche at the age of 17, followed by an irregular period for 2 years. Her menstrual cycles lasted 42 to 56 days and menstrual period lasted 1 to 5 days. Meanwhile, the patient also noticed gradually mild graying and loss of hair. She was diagnosed with "polycystic ovary syndrome (PCOS)" at another hospital and treated with traditional Chinese medicine along with Ethinyl Estradiol and Cyproterone Acetate tablets for 3 months, but the symptoms were not improved. She presented to our division because of a suddenly shortened menstrual cycle to 35 days and elevated fasting and postprandial blood glucose levels. Symptoms of diabetes such as polydipsia, polyphagia, or polyuria were not noticeable.

The patient was normal at birth and during childhood. She grew and developed healthy till 13 years old, apart from the absence of a pubertal growth spurt. She seemed to have delayed puberty compare to same-age peers. The parents were non-consanguineous and both had normal growth and development. The height and weight of her father were 178 cm and 80 kg, respectively, and the height and weight of her mother was 168 cm and 75 kg, respectively.

The physical examination revealed the graying and thinning of scalp hair, sparse axillary and pubic hair with female distribution, and a pinched and bird-like facial appearance with slightly protruding eyes and beaked nose. There was also diffuse pigmentation of skin on her face and extremities (Fig. 1, A(1)), thinner and atrophic skin over the hands and feet with apparent subcutaneous vessels, and lipoatrophy of the extremities, especially the hands and the feet (Fig. 1, A(2), A(3)). No physical signs of body fat redistribution was noted. She had underdeveloped breasts at Tanner stage 3. No cataracts, hearing abnormity, abnormal tooth alignment, hirsutism, clitoromegaly, skin ulcers, corns or calluses were detected. The blood pressure was normal. The height and weight of the patient was 160 cm and 44 kg, respectively. The body mass index (BMI) was 17.20 kg/m^2. She had short stature compared with the parents.

Main laboratory test results were shown in Table 1. A high testosterone level and follicle-stimulating hormone (FSH)/luteinizing hormone (LH) ratio and a low progesterone level was found 3 months ago before any treatment. On Day 2 of the menstrual cycle when she was admitted, the patient had decreased estradiol and progesterone levels. Routine tests were normal. Lipid test revealed hypertriglyceridemia. Insulin-resistant DM was present in the patient due to the elevated blood glucose and insulin levels. Pituitary, adrenal, and thyroid functions were normal. Antinuclear antibodies and rheumatoid factor were negative. Visceral fat area, whole-body fat percentage and lean mass measured by dual-energy X-ray absorptiometry were 131.6 cm^2, 10.7% and 39.29 kg. Gynecologic ultrasound examinations carried out 3 months and 2 days before admission revealed polycystic ovarian morphology and ovarian cyst. Abdominal ultrasonography indicated fatty liver. Arterial ultrasound, bone age and bone mineral density assessment showed no abnormalities. Her parents had normal blood glucose levels and islet function. With approval of Committee on Biomedical Ethics of The First Hospital of Jilin University (2018-340), and the consent of the patient, genetic analysis was carried out.

Results

Genetic analysis of *WRN* gene revealed a synonymous mutation c.513 C>T in exon 6 and a missense mutation c.3222 G>T (p.L1074F) in exon 26 (Fig. 1, B). Both mutations showed no clinical significance after searching the ClinVar database. Therefore, whole-exome sequencing aimed at all the suspected diseases was performed and two novel missense mutations were identified in *LMNA*, including c.419T>A (p.L140Q) in exon 2 (Fig. 1, C(1)) and c.1016C>T (p.A339V) in exon 6 (Fig. 1, C(2)). The former mutation with a different amino acid substitution (p.L140R) was previously reported to cause AWS in The Lancet in 2003 [4]. The c.419T>A (p.L140Q) was a wild-type mutation and the clinical significance of this mutation was unclear. Genetic sequencing of *LMNA* demonstrated that her father was a carrier of the c.419T>A (p.L140Q) (Fig. 1, C(3), C(4)), while no mutation was found in her mother (Fig. 1, C(5), C(6)).

Discussion

Polycystic ovary syndrome (PCOS) was suspected,

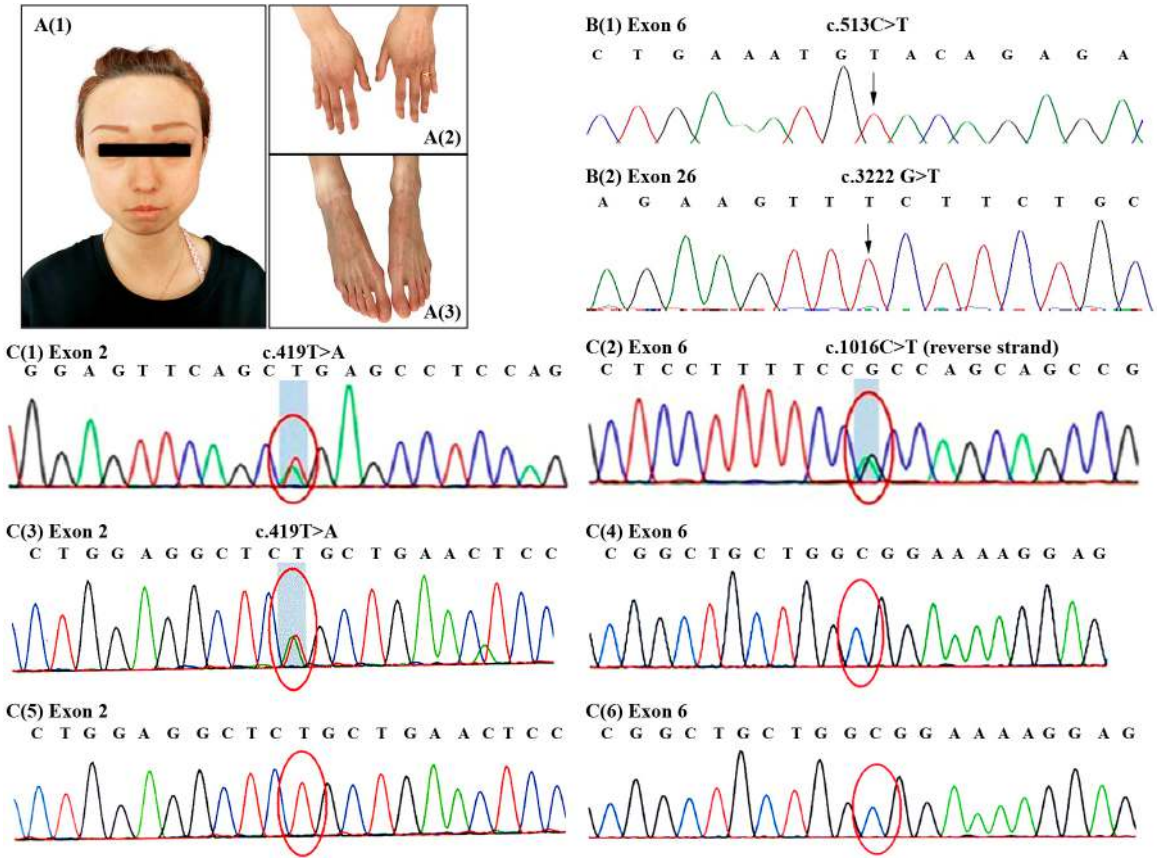

Fig. 1 A: The face of the patient was shown in A(1), she looked older than her chronological age, bird-like facial appearance, diffuse pigmentation of the skin. Lipoatrophy of extremities was shown in A(2) and A(3), the skin was the thinner and atrophic, subcutaneous vessels were obvious. B: Genetic analysis of *WAN*. B(1): Synonymous mutation c.513 C>T in 6 exon. B(2): Missense mutation c.3222 G>T in 26 exon, leads to p.L1074F. The mutant nucleotides are marked with an arrow. C: Genetic analysis of *LMNA*. Patient: Mutation c.419T>A in exon 2 (C(1)), leads to p.L140Q, c.1016C>T in exon 6 (C(2)), leads to p.A339V; Father: Mutation c.419T>A in exon 2 (C(3)), No mutation in exon 6 (C(4)); Mother: no mutation of *LMNA*(C(5), C(6)). The mutant related nucleotides and the same position are marked with a circle.

but the second sex hormone test performed after she was admitted to our division showed only decreased estradiol and progesterone levels, whereas FSH and LH levels did not increase accordingly by the negative feedback loop regulation, indicating the presence of secondary hypogonadism, so PCOS was excluded. The patient had insulin-resistant DM even though she had no family history of DM and suffered generalized lipoatrophy. She had experienced absent pubertal growth spurt, late age at menarche in relative to her peers, and underdeveloped breasts. Moreover, she looked older than her peers, had special "bird-like" appearance, and experienced loss and graying of hair indicative of progeria. Above all, an admitting diagnosis of "possible" WS was made according to the diagnostic criteria of WS. Majority of WS is caused by mutations of the *WRN* gene, and therefore, genetic analysis of the *WRN* gene was performed, but the result was negative. Whole-exome sequencing aimed at all the suspected diseases, such as Hutchinson-Gilford Progeria syndrome, familial partial lipodystrophy, limb-girdle muscular dystrophies, Emery-Dreifuss muscular dystrophy, *et al.*, was carried out, the pathogenic mutation p.L140Q in the *LMNA* gene was found, leading to the diagnosis of AWS. Genetic sequencing of *LMNA* gene for her parents confirmed her father to be the pathogenic carrier, suggesting that AWS is a hereditary disease.

LMNA gene encodes lamin A and C, which constitute an intermediate filament protein attached to the inner membrane of the nuclear envelop, and are important in regulating gene transcription and cell mitosis [8, 9]. Therefore, *LMNA* mutation affects multiple organs and tissues. The primary clinical sign of our patient was lipoatrophy. The lipoatrophy caused by *LMNA* mutations leads to dysfunction of adipocytes, resulting in reduced fat storage, and decreased leptin and adiponectin levels, while increased free fatty acids. Excess triglyceride may accumulate in the liver and skeletal muscles contributing to insulin resistance, hypertriglyceridemia, and hepatic

Table 1 Laboratory data of the proband

Variable	test value	reference range
Oral glucose test		
FPG (mmol/L)	8.15	3.9–6.1
2hPPG (mmol/L)	17.34	3.9–7.8
Fasting plasma insulin (pmol/L)	681.7	17.0–173.0
2h postprandial plasma insulin (pmol/L)	2,079	
ICA	negative	
IAA	negative	
GADA	negative	
IA2A	negative	
HbA1C (%)	7.9	4.27–6.07
IGF-1(ng/mL)	369	141–483
TG (mmol/L)	6.05	0.28–1.80
FSH (mIU/mL) (3 months ago)	5.58	1.79–5.12
LH (mIU/mL) (3 months ago)	12.03	1.20–12.9
PRL (mIU/L) (3 months ago)	148.9	20.8–556.5
PG (nmol/L) (3 months ago)	3.9	16.4–59.0
T (nmol/L) (3 months ago)	2.17	0.20–1.65
E2 (pmol/L) (3 months ago)	193	180–1,068
FSH (mIU/mL)	4.230	3.85–8.78
LH (mIU/mL)	6.100	2.12–10.89
PRL (mIU/L)	463.54	70.81–566.5
PG (nmol/L)	0.98	0.99–4.83
T (nmol/L)	1.010	<0.35–2.60
E2 (pmol/L)	<73.0	99.09–447.7

FPG, fasting plasma glucose; PPG, postprandial plasma glucose; ICA, islet cytoplasmic autoantibodies; IAA, Insulin autoantibodies; GADA, glutamic acid decarboxylase; IA2A, tyrosine phosphatase-protein antibodies; HbA1C, glycosylated hemoglobin; IGF, insulin growth factor; TG, triglyceride; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; PG, progesterone; T, testosterone; E2, estradiol.

steatosis. Initially, hyperinsulinemia may compensate for insulin resistance to maintain euglycemia, but the overload of β-cells may eventually cause hyperglycemia. Meanwhile, high levels of insulin stimulate insulin-like growth factor 1 receptor, resulting in polycystic overy, even PCOS, that can lead to menstrual disorder and infertility [10]. In addition, mutations in *LMNA* gene are also responsible for primary and secondary hypogonadism, leading to menstrual disorder and infertility [11]. One of the limitations in this study was that serum leptin, adiponectin level were not assessed.

The major symptoms of our 19-year-old patient were irregular menstruation and DM, while the average age of onset for hypogonadism and DM in WS (mainly CWS) patients was 35.6 and 31.5 years old, respectively [11]. There may be differences between classic and atypical WS. Therefore, We used "atypical Werner syndrome", "Werner syndrome" and "*LMNA* mutation", "progeria" and "*LMNA* mutation" to search in English database (Medline), and Chinese database (China National Knowledge Infrastructure (CNKI) and WANFANG MED ONLINE) up to 31st August 2018, and found 9 patients with AWS reported by 7 articles [4, 5, 9, 12-15]. Demographic (*i.e.*, age, gender, race, genotypes of AWS) and clinical characteristics of individual patients were summarized in Table 2. In addition, Table 3 summarized the features of AWS and CWS as the following [3, 4, 6, 11, 16-19]:

Pathogenesis: AWS is an autosomal dominant disease partially caused by *LMNA* mutation, which mainly occurs in exon 2 (50%) and exon 5 (30%). *LMNA* mutations can be inherited from the father (40%) and from the mother (10%). While, CWS is an autosomal recessive disease caused by homozygous or compound hereozygous mutations at the *WRN* gene, which encodes a member of RecQ family of DNA helicase. The dysfunction of *WRN* gene can lead to DNA damage such as deficient in DNA replication and repair, as well as genomic instability and telomere attrition resulting in reduced cell proliferation telomerase activity, and premature senescense, limited replicative lifespan and telomere length/synthesis. It have been reported that, although AWS and CWS differ in their pathogenesis, they have overlapping clinical phenotypes, possibility in part due to impaired *WRN* function or various *WRN* interacting proteins in AWS patients. Moreover, clinical discordances of WS may be attributed to single nucleotide polymorphisms in both *WRN* and *LMNA* gene, along with differential expressions and regulations of gene-related proteins in various cell types and tissues. Additionally, the presence or absence of the compensatory enzymes or signal transduction pathway among various tissues may also play an important role in the pathogenesis of the disease.

Prevalence: the incidence of AWS is much lower than the rates of CWS. Sixty percent of AWS patients were Asian (Chinese, Japanese, Korean, and Middle Eastern) and 80% of CWS patients were Japanese. The incidence of WS in Japanese were 10–100 times higher than in non-Japanese.

Male to female ratio: that of AWS was 2:3, of CWS was 3:2.

Age of onset and death: usually, AWS patients have an early onset of pathology compared to patients with CWS. It was reported that the onset age for AWS ranged from 10 to 66 years old, which ranged from 15 to 53 years old in our summary. Ninety percent of the AWS patients

Table 2 The Features of Reported Patients with AWS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Sex	F	F	M	F	M	F	M	F	M	F
Age at diagnosis	18	18	34	23	31	15	53	18	24	19
Race	African-American	Caucasian	European	Middle Eastern	France	Korean	Japanese	Chinese	Chinese	Chinese
Gene	Exon 2 R133L	Exon 2 R133L	Exon 2 L140R	Exon 1 A57P	Exon 5 D300N	Exon 2 T506del	Exon 5 D300N	Exon 9 L512P	Exon 5 D300H	Exon 2 L140Q
Age of initial symptoms	17	9	14	Early teens	NA	13	50	13	23	17
Initial presenting symptoms	Fatigue, thinning and graying of the hair	Short stature	Defined as being physically inferior	Short stature	Acute onset right hemiplegia and aphasia	Abdominal distension and an elevated blood glucose level	Sclerodactyly, toe ulcers for 3 years	Growth retardation	Cerebral hemorrhage	Irregular menstruation
Cardinal signs and symptoms (positive ratio)										
1. Cataracts (10%)	N	N	Y	N	N	N	N	N	NA	N
2. Dermatological pathology (100%)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bird-like faces with a beaked nose (70%)	Y	Y	NA	NA	Y	Y	N	Y	Y	Y
3. Short stature (70%)	Y	Y	N	Y	Y	N	Y	Y	N	Y
4. Parental consanguinity (0%)	NA	NA	NA	NA	NA	NA	N	N	NA	N
Affected sibling (0%)	NA	NA	NA	NA	N	N	Y	N	NA	N
5. Premature greying (50%)	Y	Y	Y	Y	NA	N	N	N	N	Y
6. Thining of scalp hair (90%)	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y
Further signs and symptoms (positive ratio)										
1. DM (50%)	Y	Y	N	N	NA	Y	N	Y	NA	Y
2. Hypogandism (60%)	N	Y	Y	Y	NA	NA	NA	Y	Y	Y
3. Osteoporosis (60%)	NA	Y	Y	Y	Y	NA	Y	NA	Y	N
4. Osteosclerosis of distal (10%)	NA	NA	NA	Y	NA	NA	NA	NA	NA	N
5. Soft tissue calcification (40%)	NA	N	Y	N	Y	NA	Y	NA	Y	N
6. Atherosclerosis (40%)	NA	N	Y	N	Y	NA	Y	NA	Y	N
7. Neoplasms (0%)	NA	N	N	N	NA	NA	N	N	NA	N
8. Voice change (50%)	NA	Y	Y	N	NA	NA	Y	Y	Y	N
9. Flat feet (10%)	NA	NA	NA	NA	NA	NA	NA	Y	NA	N
Other features	Father inheritance	NA	Aortic stenosis/ insufficiency; died at age 36 years	Dilated cardiomyopathy; sloping shoulders	Father inheritance	Mother and sister carry the pathologic gene	Father inheritance; combined valvular disease; arrhythmia	NA	NA	Father carries the pathologic gene
Diagnosis based on criteria of WS	Possible	Possible	Possible	Possible	Possible	—	Possible	Possible	Possible	Possible
References	[4, 5]	[4, 5]	[4, 5]	[4, 5]	[12]	[13]	[14]	[15]	[9]	The present study

Y, yes; N, no; NA, not applicable. The patients above include 9 patients with AWS reported in 7 articles, in addition to the patients with AWS we reported. All diagnosis were confirmed by genetic testing with the analysis of the *LMNA* gene.

Table 3 Similarities and differences between CWS and AWS

	CWS	AWS caused by LMNA mutation
Responsible gene (incidence)	Mutations at *WRN* (70%), which encodes a member of RecQ family of DNA helicase, leading to the loss of function in the DNA replication, DNA repair, and telomere maintenance	Mutations at *LMNA* (5%), which encodes nuclear intermediate filaments, lamin A and C, leading to cell instability and ultimately tissue atrophy
Inheritance	Autosomal recessive (AR)	Autosomal dominant (AD)
Vulnerable races	Japanese	Asia (Chinese, Japanese, Korean, and Middle Eastern)
Male to female ratio	3 to 2	2 to 3
Age of onset (year)	Teens or 20s	Range from age 10 to 66 years
Age (year) and main causes of death	54.3 (median age of death) Myocardial infarction and malignancy	NA
Clinical features (incidence, age (year) at which the manifestations were observed)		
Bilateral cataracts	99%, 31.2 ± 8.5	10%, 34
Characteristic dermatologic changes	96%, 26.4 ± 10.1	100%, 25.3 ± 11.48
Short stature	95%, 18.9 ± 7.7	70%, 24.9 ± 12.2
Parental consanguinity and affected sibling	51% and 39.4%	0% and 10%
Premature graying and/or thining of scalp hair	100%, 20.1 ± 10.4	Premature graying 50%, 22.4 ± 6.8; thining of scalp hair 90%, 24.7 ± 12.0
Diabetes mellitus	71%, 31.5 ± 9.0	50%, 17.6 ± 1.5
Hypogonadism	80%, 35.6 ± 8.4	60%, 22.7 ± 6.1
Osteoporosis	91%, 39.5 ± 7.55	60%, 30.5 ± 12.4
Osteosclerosis of distal phalanges of fingers and/or toes	NA	10%, 23
Soft tissue calcification	67%, NA	40%, 35.5 ± 12.4
Atherosclerosis	30%, 40.6 ± 9.0	40%, 35.5 ± 12.4
Neoplasms	44%, 41.3 ± 9.2	0%
Voice changes	89.0%, 22.8 ± 12.1	50%, 29.4 ± 14.7
Flat feet	94.6%, n.m.	10%, 18
Diagnosis	90.9% of affected individuals had all four cardinal signs	90% of affected individuals were diagnosed with “possible” WS

WS, werner syndrome; AWS, atypical werner syndrome; NA, not applicable.

were before age of 35 years at the time of diagnosis and 50% of the patients were diagnosed between 10 and 20 years of age. The onset age for CWS was teens or 20s. The average death age for AWS were not known, and the median age of death for CWS was 54.3 years old, usually caused by myocardial infarction and malignancy.

Clinical features: (1) The incidence and the observed age of characteristic dermatologic changes in AWS (Incidence: 100% at age 25.3 ± 11.48 years) and CWS patients (incidence: 96% at age 26.4 ± 10.1 years) were similar. The incidence and age of onset of atherosclerosis was slightly higher and earlier in AWS patients (incidence: 40% at age 35.5 ± 12.4 years) than that in CWS patients (incidence: 30% at age 40.6 ± 9.0 years). Hence, we hypothesize that atherosclerosis-related diseases may be the major cause of death in AWS patients. Compared to patients with CWS, those with AWS showed much lower incidence of cataracts (10% *vs.* 99%), short stature (70% *vs.* 95%), premature graying and/or thinning of scalp hair (50–90% *vs.* 100%), DM (50% *vs.* 71%), hypogonadism (60% *vs.* 80%), osteoporosis (60% *vs.* 91%), soft tissue calcification (40% *vs.* 67%), neoplasms (0% *vs.* 94.6%), voice changes (50% *vs.* 89.0%), and flat feet (10% *vs.* 94.6%). The age of onset for cataracts in

AWS (34 years old) and CWS (31.2 ± 8.5 year-old) patients was similar. Short stature (18.9 ± 7.7 years old *vs.* 24.9 ± 12.2 years old), voice changes (22.8 ± 12.1 years old *vs.* 29.4 ± 14.7 years old), and premature graying and/or thinning of scalp hair (20.1 ± 10.4 years old *vs.* 22.4 ± 6.8 and 24.7 ± 12.0 years old) occurred earlier in patients with CWS than that in patients with AWS. In contrast, DM (17.6 ± 1.5 years old *vs.* 31.5 ± 9.0 years old), hypogonadism (22.7 ± 6.1 years old *vs.* 35.6 ± 8.4 years old), and osteoporosis (30.5 ± 12.4 years old *vs.* 39.5 ± 7.55 years old) occurred earlier in patients with AWS than that in patients with CWS. Ten percent of AWS patients had affected sibling, while 51% and 39.4% of CWS patients had parental consanguinity and affected sibling, respectively. In AWS patients, 70% had bird-like faces with a beaked nose, 10% developed osteosclerosis of distal phalanges at age 23 years old. The average age of onset of soft tissue calcification and flat feet were 35.5 ± 12.4 years old and 18 years old, respectively. (2) Overall, 60% of AWS patients began to develop initial clinical symptoms between 10 and 20 years of age. The initial signs and symptoms of AWS patients widely varied, including short stature, growth retardation, and thinning and graying of the hair as well as cerebrovascular diseases, dermatological pathology, DM, and irregular menstruation. While, in CWS patients, the initial signs were the lack of growth spurt until 18 years old and a relatively short stature as adults.

Diagnosis: lack of growth spurt and short stature may be the first sign of both AWS and CWS, but AWS patients may begin to develop initial clinical symptoms earlier than CWS patients. Characteristic dermatological pathology, but not the bilateral cataracts, may be significantly more important for initial identification of AWS. According to the diagnostic criteria of WS, almost all AWS cases were diagnosed with “possible” WS and subsequently confirmed by genetic testing, but 90.9% of CWS patients had all four cardinal signs at initial diagnosis. The incidence of clinical manifestations was lower in AWS than in CWS and the incidence of AWS itself was much lower than CWS, making its diagnosis even more difficult.

The possible mechanisms of insulin resistance in WS patients (both CWS and AWS) include reduced insulin receptors in fat cells, loss of signal transduction after the binding of normal insulin to normal receptors, and defected post-receptor step [11, 19]. The physical activity reduced for sarcopenia in WS patients may be one cause for accumulation of visceral fat, resulting in insulin resistance [20]. In addition, dysregulation of adipocytokine may be another mechanism for the development of DM in WS patients. In addition, AWS patients usually have higher rates of disease progression and much more severe insulin resistance compared to CWS patients [11, 16].

Clinical manifestations, laboratory test results, and genetic analysis are critical in the diagnosis of WS. In the current cases, clinical characteristics of the patient provided important clues to a possible diagnosis of WS, which were ultimately confirmed by genetic analysis of *WRN* and *LMNA* genes. Additionally, dermatological pathology may be the initial presentation of WS and can be used to stage the degree of WS through various biophysical parameters, including roughness, skin barrier function, skinfold thickness, and epidermal and glandular atrophy [5, 21]. Protein analysis on progeria-related proteins such as *WRN* protein, progerin, and other mutant forms of lamins, as well as immunofluorescence analysis on lamin A/C in skin fibroblasts may be useful tools for the diagnosis of both CWS and AWS when pathogenic alleles cannot be identified by sequence analysis [6, 13, 22, 23]. One limitation of this study was the lack of analysis at protein level to make a better understanding of WS.

We carried out therapy for lowering blood glucose and improving insulin resistance (pioglitazone, 30 mg, once per day), lipid (fenofibrate, 200 mg once per day), vitamin C (300 mg, 3 times per day), excellent skin care, trauma avoidance may prevent skin damages. The fasting glucose was 6 to 7 mmol/L, postprandial glucose was 6 to 11 mmol/L, triglyceride was 3.12 mmol/L after treatment for 9 days with no adverse effects. In addition, treatment of malignancies, osteoporosis, and hypogonadism should be a top priority for patients with WS [6]. Administration of a specific adipokine, such as leptin, and transplantation of subcutaneous fat may induce sustained improvements in hyperglycemia, dyslipidemia, and hepatic steatosis caused by lipodystrophies [24]. It is alternative to use surgery for refractory ulcers of WS [25] and cataract [16], anti-aging treatment such as vitamin C [26], rapamycin [17] or combined with farnesyltransferase inhibitor [27], pluripotent stem cell [28, 29]. Annual screening for tumor and cataracts is important for early detection of the complications, especially in patients with CWS. Similarly, attention must be paid/given to arteriosclerosis-related diseases in WS patients, particularly in AWS patients [6, 17]. In the future, multiomics technologies, including genomics, epigenomics, and transcriptomics as well as proteomics and metabonomics are expected to provide new approaches for the prevention and treatment of aging-related disorders [29].

Conclusions

We reported a young female patient presented with DM and progeria. She was diagnosed with AWS caused

by a novel *LMNA* mutation (c.419T>A, p.L140Q), which was inherited from her father. WS is a rare inherited disease characterized by progeria. It was reported that 5% of patients with WS was caused by *LMNA* mutation and was categorized as AWS. Classic and atypical WS differ in several aspects such as pathogenesis, incidence, and clinical manifestations. Characteristic dermatological pathology may be especially important for the initial identification of AWS, but not the bilateral cataracts. Genetic analysis is critical in the diagnosis of WS. The mechanisms, clinical features, and diagnostic methods as well as treatments of WS require further studies. Early diagnosis, proper treatment, and regular follow-up may improve the overall prognosis of WS.

Declaration of Conflicts of Interests

The authors have nothing to disclose.

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Ethic Approval and Consent to Participate

This study involving Human Participants was approved by the ethical review committee of The First Hospital of Jilin University (2018-340). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Consent for Publication

Written informed consent was obtained from the patient prior to the use of her data and images for publication.

Availability of Data and Materials

All clinical data to support this case are available from the corresponding author upon reasonable request.

Authors' Contributions

GH designed the study, GH and XG acquired the data and drafted the initial manuscript, LS, ZY and YL assisted in literature collection, XG, ZY and WG assisted in editing the manuscript, GW supervised the whole study.

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