Case Report

A case of premature aging with recurrent pancreatitis and lipodystrophy

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ABSTRACT

Werner's syndrome (WS) is characterized by insulin resistance along with signs of premature aging. It poses great diagnostic challenge because of its unusual presentation. We describe a case of WS in a 30-year-old female, who presented with recurrent pancreatitis and documented hypertriglyceridemia along with hyperglycemia despite getting more than 200 units of insulin per day, without any history of hyperglycemic emergency such as diabetic ketoacidosis (DKA)/ hyperglycemic hyperosmolar state (HHS). Examination showed signs of premature aging (alopecia, progressive sharpening of facial features, loss of upper incisor teeth, wrinkles and freckles) and generalized wasting. Scalp biopsy confirmed the diagnosis.

Key words: *Werner's syndrome, pancreatitis, hypertriglyceridemia, autoimmune polyglandular syndrome, type B insulin resistance syndrome.*

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INTRODUCTION

Werner's syndrome (WS) was initially described by Werner in 1904.[1] WS is an autosomal recessive disorder, caused by loss-of-function variants of the *WRN* gene on chromosome 8p12, characterized by multiple features consistent with accelerated aging.[2,3] The incidence is 1 per 10,000 to <1 per 100,000 births with geographic and family clustering in Japan, Sardinia, India and Pakistan.[4] Clinical characteristics include short stature, senile appearance, cataract, early menopause, premature arteriosclerosis, skin changes (scleroderma-like features, premature canities, baldness and skin ulceration) and associated with an increased risk of malignancy.[5] The WS skin is quite similar to aged skin, a patient of 30 years of age has the same skin roughness of a 50/60 years old with decrease in skin structure leading to an epidermal and dermal atrophy.[6,7] The diagnosis, management, course and prognosis of the disease remain highly enigmatic. In view of this situation, we report a confirmed case of WS in a 30-year-old Bangladeshi female patient.

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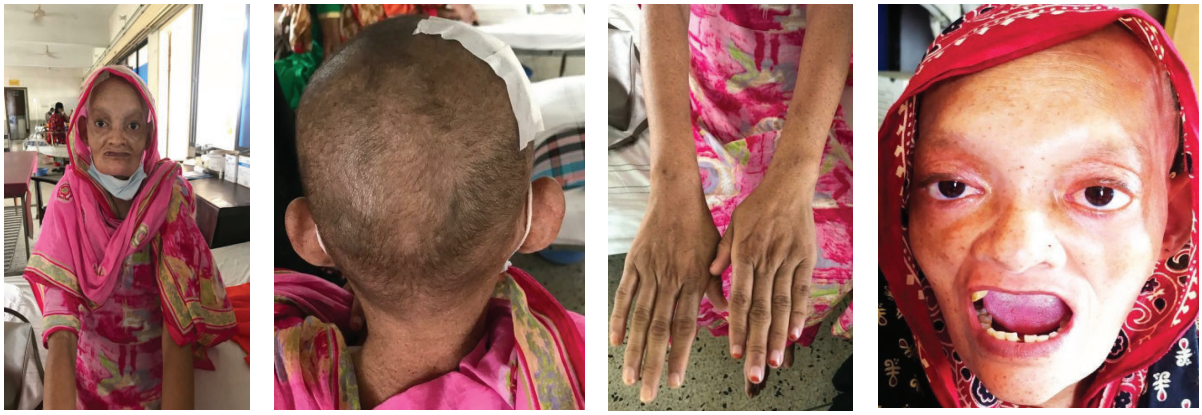
CASE REPORT

A 30-year-old lady, diabetic for 17 years, hypothyroid for 10 years, hypogonadal for 4 years, presented with upper abdominal pain that was dull aching in nature, moderate to severe in intensity, radiated to upper back without any relieving or aggravating factors, associated with vomiting 3-4 times in a day. Vomitus contained undigested food particles without any bile or blood. On query, she gave history of occasional passage of loose stool with oil spotting. Her blood glucose was grossly uncontrolled despite taking total 228 units of insulin per day. She also complained of excessive fall of hair and loss of teeth. There was no history of taking any non-steroidal anti-inflammatory drugs, steroids, oral ulcers, joint pain, heart burn, Raynaud's phenomenon or skin rash.



(a) (b) (c) (d)

Figure 1. (a) Prematurely aged face, (b) alopecia with scalp biopsy bandage, (c) generalized wrinkles and freckles and (d) loss of incisor teeth and loss of eye brows and eyelashes

She had two previous episodes of hospital admissions for upper abdominal pain due to pancreatitis associated with hypertriglyceridemia. There was no consanguinity of marriage in her parents. Both of her parents are diabetic; she has unaffected two brothers and one sister. She was delivered by normal vaginal delivery at term without any perinatal complications, her developmental milestone was age appropriate except lack of pubertal changes. She was on split mixed insulin since her diagnosis of diabetes, there was no acute hyperglycemic or hypoglycemic complication. She was taking levothyroxine 50 microgram daily for 10 years and hormonal replacement therapy consisted of cyclical estrogen and progesterone for last 4 years. She was amenorrheic up to age 26 years before starting hormone replacement therapy (HRT). Now her cycles are regular on HRT.

Her physical examination revealed alopecia, loss of eye brows and eyelashes, prematurely aged face with progressive sharpening of facial features, generalized wrinkles and freckles and loss of upper incisor teeth (Figure 1. a-d). Her weight 38 kg, height 149 cm, body mass index was 17.12 kg/m^2, blood pressure: 110/70 mm Hg (without any postural drop of BP). Her general skin survey showed dry skin with wrinkles and freckles, without any mucosal or pressure area pigmentation. Random blood glucose was 16 mmol/L. Bed side urine examination revealed glycosuria (++), albuminuria (+) without any ketone body. Her sexual maturation was underdeveloped (Tanner staging: breast 3, pubic hair 2).

On abdominal examination, skin was slightly tight, shiny with freckles all over the skin. Mild epigastric tenderness was present on palpation, remaining findings was within normal limit. Nervous system examination showed generalized wasting with loss of arch of feet. Fundoscopic examination revealed dot blot hemorrhage with previous laser marks in peripheral retina.

Her investigations revealed pancreatitis as evidence by elevated amylase (215 U/L) and lipase (210 U/L). Her blood glucose profile shows HbA1c 13.8%, fasting 12.4 mmol/L, 2 hours after breakfast 16.9 mmol/L, before lunch 15.4 mmol/l, 2 hours after lunch 18.6 mmol/L, before dinner 14.0 mmol/L and 2 hours after dinner 19.6 mmol/L. Complete blood count, renal function, liver function, urine routine examination, ECG, echocardiography were within normal limit. Serum electrolytes showed hypokalemia (K^+ 3.2 mmol/L). Ultrasonogram of whole abdomen revealed mild fatty change in liver. Autoimmue screening was negative. Karyotype was 46XX. Table I demonstrates lipid profile across admissions, Table II shows hormonal investigation. Microscopic examination of skin biopsy showed thin epidermis with loss of rete ridges, dermis revealed fibrosis and less number of adnexal structures, subcutaneous fatty tissue ws also fibrotic. Features were compatible with progeria of adult (Werner's syndrome).

Table I. Lipid profile of the patient with Werner's syndrome in different admissions

Components	Year 2012 First episode of pancreatitis	Year 2017 Second episode of pancreatitis	Year 2021 During this admission with pancreatitis	Normal ranges (mg/dl)
Total cholesterol	256	232	159	Up to 200
HDL-C	40	24	22	Female > 55
LDL-C	90	64	63	<140
Triglycerides	2554	1355	607	50-150

Table II. Hormonal investigation reports of the patients with Werener's syndrome

Thyroid function test	Normal ranges
TSH 7.9 uIU/ml	0.47 - 5.01 micro IU/ml
Free T_4 8.16 pmol/L	9.14 - 23.18 pmol/L
Anti-TPO antibody 89.5 (mildly positive)	Anti-thyroid peroxidase Ab>60 U/ml positive
Anti-TG antibody 28.2 (mildly positive)	Anti-thyroglobulin Ab> 4.5 IU/ml positive
Parathyroid function test	Normal ranges
Serum (i) PTH 19.99 pg/ml	7 - 53 pg/ml
Serum corrected calcium 9.5 mmol/L	8.4 - 10.4 mg/dl
Adrenal function test	Normal ranges
ACTH 19 pg/ml	8.3 - 57.8 pg/ml
Basal cortisol 486.55 nmol/L	101.2 - 690 nmol/L
Gonadal function test	Normal ranges
Serum FSH 33.49 mIU/ml	Follicular phase 3.03 - 8.08 mIU/ml
	Postmenopausal 26.72 - 133.41 mIU/ml
Serum LH 17.17 mIU/ml	Follicular phase 1.8 - 11.78 mIU/ml
	Postmenopausal 5.16 - 61.99 mIU/ml
Serum oestradiol 21.830 pg/ml	Follicular phase 21 - 160 pg/ml
	Postmenopausal < 32.20 pg/ml

After exclusion of autoimmune polyglandular syndrome, type B insulin resistance syndrome, Turners syndrome and considering all the clinical, biochemical and skin biopsy findings, WS was diagnosed. Initially patient was managed by intravenous fluid, potassium replacement and intravenous insulin pump, after improvement of her general condition subcutaneous split mixed short acting regular and NPH insulin (total dose was 110 units/day) along with oral pioglitazone 15 mg once daily was started. Her hypertriglyceridemia was managed with fenofibrate 200 mg once daily, levothyroxine dose was increased to 75 microgm/day, hormone replacement therapy was continued with cyclical estrogen and progesterone, pancreatic enzyme supplementation with proton pump inhibitor was also continued. She is now on regular follow up at outpatient department.

DISCUSSION

WS is common in Japan and Sardinia in Italy. Most of cases are reported in consanguineous marriage but there are also few cases in non-consanguineous marriage. This is because a genetic mutation was known to occur many generations ago, when their population was smaller in number and over time the genetic mutation has been passed down repeatedly, affecting a higher number of people; this is called a founder mutation.[8] In our case, there was no consanguineous marriage.

Premature graying and/or thinning of scalp hair, bilateral cataract, scleroderma-like skin changes, intractable lower leg skin ulcers, soft tissue calcification, bird-like face, high-pitched voice are the cardinal signs of WS.[5] In our patient there were all of the mentioned criteria except cataract, leg ulcers and calcification. Expression of all features of WS may occur only two or three decades after an initial diagnosis in the second decade.

The adult onset and slow development of clinical signs and symptoms make the clinical diagnosis of it challenging and often delayed. Diagnostic suspicion of WS is driven by considering the aging signs in light of patient age along with cardinal signs and additional findings of WS. Genetic testing is required to identify both copies of *WRN to* confirms the diagnosis.[3] We could not do the genetic testing due to limited resource but confirmed the diagnosis by the histopathological findings.

There is no specific treatment of WS. Treatment is driven by associated complications (leg ulcers, cataract, osteoporosis), co-morbidities and need regular surveillance for malignancy.[5]

We managed our patient's acute complication such as pancreatitis and chronic co-morbidities like diabetes with insulin and pioglitazone, hypertriglyceridemia with fibrates, hypogonadism with HRT and hypothyroidism with levothyroxine.

Conclusion

Unusual premature aging signs along with insulin resistance and hypertriglyceridemia, even in absence of family history of similar illness or consanguineous marriage needs to explore properly. High index of suspicion and extensive investigations are required to diagnose WS.

Authors' contribution: MD was involved in the diagnosis, patient management, manuscript writing and literature review. MAI helped in editing. All authors were involved in evaluation and management of the case.

Conflicts of interest: Nothing to declare.

Consent: Informed written consent was taken from the patient for publication of this case report and accompanying images.

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