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Case Report

Alström Syndrome: A Rare Cause of Severe Insulin Resistance

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Abstract

Diabetes mellitus is one of the most common diseases worldwide and is a major cause of morbidity and mortality. Type 2 diabetes, with its hallmark being insulin resistance, constitutes the majority of cases. Although usually related to modifiable risk factors, insulin resistance can have genetic causes. Here, we present one of the rare causes of insulin resistance. A 21-year-old man, who was deaf and blind, presented with a 3-week history of polyuria and polydipsia. He was found to have significant hyperglycemia, managed initially with insulin infusion, then he was transitioned to subcutaneous injections. Because he required high doses of insulin and had acanthosis nigricans, insulin resistance was suspected. Putting together his insulin resistance and chronic history of syndromic features, Alström syndrome was considered. Genetic testing revealed a mutation in the *ALMS1* gene. The patient was then started on insulin sensitizers with a tapering of insulin with good response. Insulin resistance should be suspected if the insulin requirement is high and if acanthosis nigricans is present. Alström syndrome is a rare causes of insulin resistance. Affected individuals will usually have insulin-resistant diabetes by a young age and associated blindness and deafness. Insulin sensitizers are an important part of the treatment.

Key Words: insulin resistance, diabetes mellitus, blindness, hearing loss, Alström syndrome

Abbreviations: ALMS, Alström syndrome; BMI, body mass index; MODY, maturity-onset diabetes of the young.

Diabetes mellitus is one of the most common diseases worldwide and one of the significant causes of morbidity and mortality. Age is an important differentiating feature between type 1 and type 2 diabetes [1]. However, the prevalence of type 2 diabetes is rapidly increasing in adolescents and young adults because of higher rates of obesity and sedentary lifestyle. Moreover, developing type 2 diabetes at a younger age has been associated with more aggressive disease and a higher risk of chronic complications [2]. The primary pathophysiology underlying type 2 diabetes is insulin resistance.

There are many causes of insulin resistance, which are classified into 2 major types. The first is acquired causes such as obesity, sedentary lifestyle, certain medications, and endocrinological diseases, like Cushing syndrome, acromegaly, and hypothyroidism. The second category includes some genetic causes like Robson-Mendenhall syndrome, type A insulin resistance syndrome, Alström syndrome (ALMS), and Werner syndrome. Here, we describe a rare cause of insulin resistance in a patient presenting with young-onset type 2 diabetes.

Case

A 21-year-old Saudi man was referred to our endocrine service for management of symptomatic hyperglycemia. He presented to the emergency department with a 3-week history of polyuria, polydipsia, and weight loss. His medical history is significant for infantile polyphagia, obesity, and gradual bilateral visual loss, caused by retinitis pigmentosa, which started at age 5 months. He went on to develop hearing loss as well as learning difficulties. Later during childhood, he was diagnosed with seizure disorder. He also has major depressive disorders and psychosis that was diagnosed 5 years before presentation. His medications are olanzapine, fluvoxamine, procyclidine, and sodium valproate. There is no family history of diabetes. Regarding consanguinity, the parents are first cousins. Our patient is the eldest of 3 siblings. Both his sisters, who are age 17 and 9 years, are healthy with no similar features. His parents are also healthy, apart from psychiatric illness in his mother. His paternal uncle is 30 years old and has seizure disorder, mental retardation, and mutism, which developed in childhood, but he is not diagnosed with any syndromes.

On physical examination, he was hemodynamically stable with a blood pressure of 129/78 mm Hg and a heart rate of 76 beats per minute. He was obese with a body mass index (BMI) of 30 kg/m^2, and a height of 145 cm, which is below the 3rd percentile. He had facial features that included deep-set eyes with a round face and greasy skin over the face and

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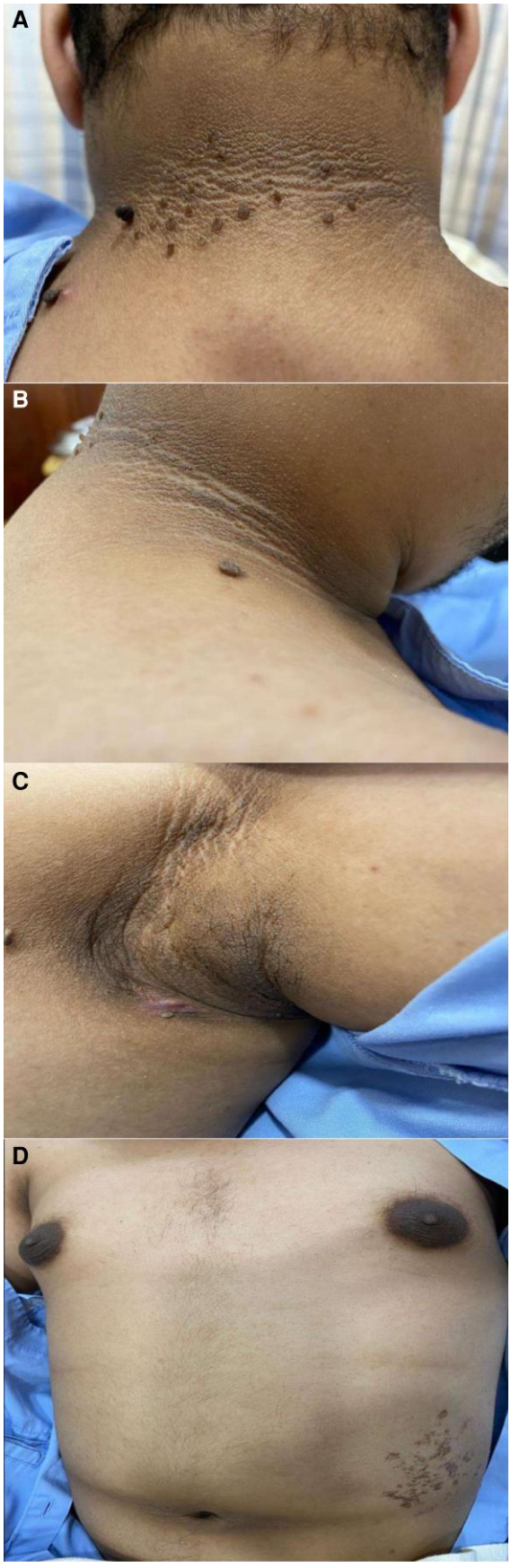

Figure 1. Photos of acanthosis nigricans, a patchy velvety brown pigmentation, in different places in our patient: (A) back of the neck, (B) lateral side of the neck, (C) axilla, and (D) around the umbilicus.

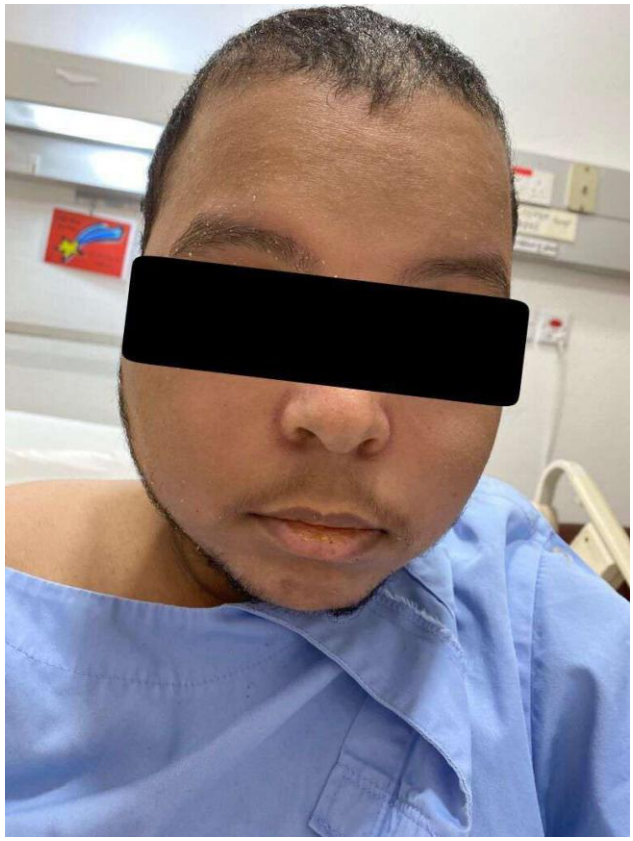

Figure 2. Photo of our patient's face showing round face and seborrheic dermatitis of the forehead, both of which are features of Alström syndrome.

the scalp. He had severe acanthosis nigricans involving the back of the neck, under his arms bilaterally, and around the umbilicus, as shown in Fig. 1. Loss of facial hair, bilateral gynecomastia, and small external genitalia were also noted. He was Tanner stage III. Over his forehead and scalp, he had seborrheic dermatitis with scales, as shown in Fig. 2. There was no evidence of polydactyly or syndactyly.

Investigations

His initial blood work revealed a very high random plasma glucose of 31 mmol/L/558 mg/dL (normal [N]: 3.9-5.6/70-100), serum bicarbonate of 22 mEq/L (N: 22-26), pH of 7.28 (N: 7.35-7.45), PCO_2 of 45.5 mm Hg (N: 35-45), serum β-hydroxybutyrate of 1.3 mmol/L (N: < 0.3) with an anion gap of 16 (N: 8-12), and serum osmolality of 305 mOsm/kg (N: 275-295). His hemoglobin A1C was 14.2% (N: < 6). Workup for secondary causes for diabetes mellitus was negative for Cushing syndrome, acromegaly, and hypothyroidism.

His total testosterone level was very low at 0.7 nmol/L/20 ng/dL (N: 10-35/300-1000) with lowish FSH and LH. His prolactin level was normal at 9.82 ng/mL/209 µg/L (N: < 20/< 425). He had impaired lipid profile with plasma triglyceride of 4.43 mmol/L/392 mg/dL (N: < 1.7/< 150), low-density lipoprotein cholesterol level of 3.3 mmol/L/128 mg/dL (N: < 3.36/< 130), and total cholesterol of 6.39 mmol/L/247 mg/dL (N: < 5/< 200). He had a mild elevation of his liver enzymes: alanine transaminase 54 IU/L (N: 7-44), aspartate transaminase 36 IU/L (5-34), alkaline phosphatase 138 IU/L

(N: 39-114), and γ-glutamyl transferase 108 IU/L (N: 11-68). His abdominal ultrasound showed mild diffuse hepatic steatosis with mild hepatomegaly. His cardiac echocardiography was normal.

Treatment and Follow-up

Our patient was started on insulin infusion because of the severe symptomatic hyperglycemia. After control of his blood sugar, he was shifted to multiple daily subcutaneous insulin injections and the doses were titrated up until he reached a total daily dose of 120 units per day to be able to control his glycemia. This is equivalent to 1.7 units/kg/d. Because of the clinical evidence of severe insulin resistance and the relatively high insulin doses, further testing was ordered to classify his diabetes. Glutamic acid decarboxylase antibody testing came back negative, and his C-peptide level was elevated at 1770 pmol/L/535 ng/dL (N: 252-1176/76-355). He was discharged home on insulin, but metformin and pioglitazone were also started at discharge.

Combining the patient's age, severe hyperglycemia, and his clinical comorbidities raised the possibility of a disorder such as Bardet-Biedl syndrome or Wolfram syndrome. However, after confirming insulin resistance, our thinking shifted toward type 2 rather than type 1 diabetes. By reviewing the literature, we found that the patient was well-matched with ALMS. Informed consent was obtained from the patient's guardians and genetic testing for *ALMS1* was done, which revealed a pathogenic homozygous variant of the *ALMS1* gene (c. 12154_12166 del).

During a follow-up 2 weeks after discharge, the patient was having recurrent episodes of hypoglycemia, so his insulin was titrated down significantly. By week 4 from discharge, he was completely off all insulin and was well controlled on his metformin and pioglitazone, and the semaglutide the was added on the first follow-up visit.

Table 1. Etiologies of insulin resistance

Causes		Clues to diagnosis
Acquired	Obesity Aging Physical inactivity High-fat diet	Presence of other features of metabolic syndrome (increased waist circumference, impaired glucose, dyslipidemia, hypertension, high inflammatory markers)
	Severe illness and stress	Patient in intensive care
	Sleep deprivation	Untreated obstructive sleep apnea
	Medications	Glucocorticoids, atypical antipsychotics, protease inhibitors
	Endocrinological diseases	Cushing syndrome, acromegaly, hypothyroidism, pheochromocytoma, polycystic ovary syndrome
Genetic	Myotonic dystrophy	Skeletal muscle weakness and myotonia
	Lipodystrophy	Absence of subcutaneous fat, and increased muscularity
	Type A insulin resistance	Severe insulin resistance with absent anti-insulin antibodies
	Type B insulin resistance	Severe insulin resistance with positive anti-insulin antibodies
	Werner syndrome	Short stature, cataracts, graying/loss of hair, scleroderma-like skin changes, hoarse voice
	Rabson-Mendenhall syndrome	Failure to thrive, premature dentition, prognathism, thick nails
	Alström syndrome	Blindness, deafness, dilated cardiomyopathy, obesity, renal failure
	Down syndrome	Upslanting palpebral fissures, epicanthic folds, brachycephaly
	Turner syndrome	Short stature, widely spaced nipples, short webbed neck, primary hypogonadism, affects females
	Klinefelter syndrome	Primary hypogonadism, gynecomastia, small testes, tall stature (increased legs-to-arms ratio), affects males
	Hemochromatosis	Liver failure, dilated cardiomyopathy, arthropathy, bronze skin, hypopituitarism

Discussion

Developing diabetes at a young age and having multiple syndromic features in our patient raised the suspicion for type 1 diabetes. However, it was unusual that he required very high doses of insulin to control his glycemia. Also, the presence of acanthosis nigricans steered us toward insulin resistance and type 2 diabetes. Other possible causes for hyperglycemia at such an age include latent autoimmune diabetes of adults and maturity-onset diabetes of the young (MODY). Patients with latent autoimmune diabetes of adults will usually have a phenotype similar to type 1 diabetes. They tend to have normal BMI with no evidence of acanthosis nigricans. They also tend to have positive antibodies and low-to-normal C-peptide level, which was not the case in our patient. On the other hand, our patient could fit the phenotype of patients with MODY, given his young age, high BMI, evidence of insulin resistance, negative antibodies, and high C-peptide level. However, MODY is autosomal dominant with a very strong family history, which our patient lacked. Therefore, we believed that insulin resistance and type 2 diabetes was the most likely cause in our patient.

Insulin resistance is defined as attenuated biological response to insulin in target tissues, resulting in decreased glucose uptake and utilization by end organs and compensatory increase in pancreatic insulin production [3]. Insulin resistance will result in multiple metabolic abnormalities including hypertension, hyperlipidemia, visceral adiposity, nonalcoholic fatty liver disease, and, eventually, type 2 diabetes [4].

Insulin resistance causes fall mainly into 1 of 2 categories: acquired (majority of cases) and hereditary. Acquired causes are mostly related to sedentary lifestyle, such as high fat-diet, physical inactivity, and obesity. Saturated fat and trans-fat, in particular, tend to cause insulin resistance. Obesity and increased adipose tissue, especially visceral adipose tissue, is a major risk factor for insulin resistance. Another cause for acquired insulin resistance is stress. This is usually seen in the catabolic stress of severe illness and is caused by activation of the hypothalamic-pituitary-adrenal axis and the resultant production of counterregulatory hormones. Both acute and

chronic sleep deprivation can cause insulin resistance through different mechanisms, including altered diurnal cortisol secretion and decreased plasma concentrations of leptin. Reduced sleep duration has been also associated with higher weight and BMI. Some endocrine disorders can also cause insulin resistance and should be considered and ruled out if the patient has other suggesting features. These disorders include Cushing syndrome, uncontrolled hypothyroidism, acromegaly, polycystic ovary syndrome, and catecholamine-secreting tumors. On the other hand, there are many less prevalent genetic causes for insulin resistance. These usually present at a much younger age compared with the acquired causes and can go undiagnosed for many years. One of these causes, which was present in our patient, is ALMS. Table 1 summarizes the different causes of insulin resistance with clues to each one.

ALMS is a rare autosomal recessive disorder resulting from a mutation in the *ALMS1* gene. Affected patients usually present with childhood obesity, progressive cone-rod dystrophy, which leads to blindness, sensorineural hearing loss, hypertriglyceridemia, hypogonadism, and multiorgan failure [5]. The disease was firstly described in a large Swedish family in 1959, and to date, 950 cases have been reported [6]. ALMS diagnosis might be difficult because some symptoms appear at birth, whereas others appear later in life. In a previous study, Marshall et al mentioned that diagnostic criteria vary according to age group [7]. In patients who are aged 15 years or older, 2 major and 2 minor criteria or 1 major and 4 minor criteria are needed to establish the diagnosis. The major criteria are positive genetic testing and visual impairment. The minor criteria are obesity, insulin resistance, hepatic dysfunction, hearing loss, renal failure, short stature, hypogonadism in males, and hyperandrogenism in females. Our patient met these criteria because he had all major and minor criteria expect for the renal failure.

Retinal dystrophy is a prominent symptom that affects 100% of patients with ALMS, and blindness is almost unavoidable by the age of 20 years. Visual problems usually appear immediately after delivery and progress slowly [6]. Insulin resistance is also a very prominent feature of ALMS, with 80% of patients over the age of 16 years developing insulin-resistant diabetes [8]. The clues to diagnosis, which were present in our patient, are acanthosis nigricans, high insulin and C-peptide levels, and increased insulin requirements. Although our patient did not have diabetic ketoacidosis, patients with ALMS can present with diabetic ketoacidosis and insulin deficiency because of the glucotoxicity [8]. Similar to our patient's findings, Gatherocole et al conducted an observational cohort analysis with 30 adult patients with ALMS and discovered that nonalcoholic fatty liver disease was common [9]. Dilated cardiomyopathy is also a common finding that affects up to two thirds of patients with ALMS [10].

More than 200 mutations have been described as causative for ALMS. The mutation our patient had (homozygous deletion in exon 20 of *ALMS1* gene [c. 12154_12166 del]) has been described before in a 10-year-old-Saudi girl presenting with insulin-resistant diabetes, blindness, and hearing loss [8].

The management of ALMS involves a multidisciplinary approach, and patients should be treated individually according to the symptoms and complications. Treatment of hyperglycemia associated with ALMS is similar to treatment of insulin resistance from other causes. The cornerstone of management is lifestyle intervention with diet and exercise. Pharmacotherapy is often needed, especially with severe insulin resistance. Insulin sensitizers, such as metformin and thiazolidinediones, have proven to be effective. Newer agents such as sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 inhibitors, and dipeptidyl peptidase-4 inhibitors can also be used [4]. For patients on insulin therapy, using concentrated insulin such as U-500, U-200 lispro, and U-300 glargine might be beneficial.

In summary, even if diabetes develops at a young age, insulin resistance should be suspected if the insulin requirement is high and if acanthosis nigricans is present. Alström syndrome is one of the rare causes of insulin resistance. Affected individuals will usually have insulin-resistant diabetes by a young age and have associated blindness and deafness by the time of diagnosis. Insulin sensitizers are an important part of the treatment, along with leading a healthy lifestyle.

Learning Points

- Insulin resistance and type 2 diabetes can present at young age. Clues to diagnosis include presence of acanthosis nigricans and high insulin requirements (>1 unit/kg/d).
- Alström syndrome can cause insulin resistance in the first 2 decades of life. Associated features include blindness and deafness.
- Insulin sensitizers such as metformin and thiazolidinediones are an important part of management of insulin resistance and can help in lowering insulin requirements.

Contribution

All authors made individual contributions to authorship. S.R. and S.N. were involved in the diagnosis and management of the case. S.N. was involved in obtaining the photos of the patient. S.R., S.B., and H.B. were involved in writing the manuscript. All authors reviewed and approved the final draft.

Conflict of Interest

The authors do not have any conflict of interest.

Informed consent was obtained from patient's guardian for publication of his case after de-identification.

Data Availability Statement

All data presented about the case are available upon request.

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