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Latent Autoimmune Diabetes in Adults Complicated by Persistent Isolated Glucosuria in the Absence of Hyperglycemia

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Abstract

Latent autoimmune diabetes in adults (LADA) is an autoimmune diabetes of adult-onset with the presence of diabetes associated autoantibodies. Familial renal glucosuria (FRG) is an inherited renal tubular disorder that causes persistent isolated glucosuria in the absence of hyperglycemia. We report a novel case of LADA and certain FRG. A 44-year-old man was admitted to our hospital for uncontrolled diabetes. Before admission, he had never suffered from diabetic coma and showed an improvement in HbA1c only with diet therapy. His HbA1c was 11.9% (107 mmol/mol), and anti-glutamic acid decarboxylase antibody was 13.0 U/mL. A glucagon stimulation test showed the decrease of insulin secretion: plasma C-peptide (CPR) 0 min, 0.69 ng/mL; CPR 6 min, 0.90 ng/mL. Analysis of genomic DNA revealed a novel heterozygous mutation in the SGLT2 coding gene, *SLC5A2* (c.875G >A, p.Cys292Tyr), which was assessed as probably damaging with a score of 0.998 (sensitivity: 0.27; specificity: 0.99) by an *in silico* analysis. Therefore, he was diagnosed with LADA and certain FRG. He has not shown any symptoms and his HbA1c improved to 6.4% (46 mmol/mol) three months after the introduction of insulin therapy. Our case clearly implies the clinical effectiveness of SGLT2 inhibition in patients with LADA.

Keywords

Latent Autoimmune Diabetes in Adults (LADA), Familial Renal Glucosuria (FRG), *SLC5A2* Mutation, Sodium-Glucose Cotransporter 2 (SGLT2), Insulin Therapy

1. Introduction

Latent autoimmune diabetes in adults (LADA) accounts for 2% - 12% of all cases

of diabetes [1] [2]. It is important to distinguish LADA from type 2 diabetes because patients with LADA have a higher probability of requiring insulin therapy due to a relatively rapid deterioration of pancreatic β -cell function compared to patients with type 2 diabetes [2]. Familial renal glucosuria (FRG) is an inherited renal tubular disorder that causes persistent isolated glucosuria in the absence of hyperglycemia [3]. It has been known that mutations in the sodium-glucose co-transporter 2 (SGLT2) coding gene, *SLC5A2*, were responsible for the disorder [4]. Herein, we report a novel case of LADA and certain FRG.

2. Case Report

A 44-year-old man was admitted to our hospital for uncontrolled diabetes for two years. His HbA1c was 12.0% (108 mmol/mol) 18 months before admission, which improved to 6.4% (46 mmol/mol) following a diet therapy for six months, and deteriorated to 12.0% (108 mmol/mol) again three months before admission. The patient had symptoms of polyuria, polydipsia, and unintended weight loss (8 kg/year). His past medical history was unremarkable and he had not taken any medication. However, the patient, his mother, and his 14-year-old son repeatedly presented with glucosuria despite normal blood glucose concentrations in their annual health check-up. There was no family history of diabetes. At the time of admission, his height was 168 cm and his weight was 57 kg; his blood pressure was normal. The patient presented with the following levels: HbA1c, 11.9% (107 mmol/mol); and anti-glutamic acid decarboxylase (GAD) antibody (measured with an enzyme linked immunosorbent assay), 13.0 U/mL (normal range, <5.0 U/mL). A glucagon stimulation test revealed the following results: plasma C-peptide (CPR) 0 min, 0.69 ng/mL; CPR 6 min, 0.90 ng/mL; plasma glucose (PG) 0 min, 102 mg/dL; PG 6 min, 123 mg/dL. He was diagnosed with LADA and was initiated on intensive insulin therapy with alpha-glucosidase inhibitors to preserve β -cell function [5]. His human leukocyte antigen (HLA) class II haplotypes were *DRB1* *04:05-*DQB1* *04:01, which was concordant with the diagnosis of LADA [6]. PG was controlled to an average of 150 mg/dL by an insulin injection and was monitored using continuous glucose monitoring. Urinary glucose and sodium levels were 15.8 g/day and 114.1 mEq/day. Analysis of genomic DNA from his blood samples revealed a novel heterozygous *SLC5A2* mutation (c.875G>A, p.Cys292Tyr). Therefore, the patient was also diagnosed with certain FRG. He has not shown any symptoms and his HbA1c improved to 6.4% (46 mmol/mol) three months after the introduction of insulin therapy.

3. Discussion

To the best of our knowledge, this is the first case report of LADA complicated by persistent isolated glucosuria in the absence of hyperglycemia. We thought that his persistent isolated glucosuria due to mutations in the SGLT2 coding gene, *SLC5A2*, assisted in maintaining glycemic control and pancreatic β -cell function.

LADA is an autoimmune diabetes of adult-onset with the presence of diabetes associated autoantibodies, which may not initially require insulin therapy [1] [2]. Turner *et al.* showed that 94% of patients with LADA required insulin therapy by 6 years, and time to insulin dependence was more rapid in patients <45 years old than in older cases [7]. The other previous study showed that the degrees of autoimmunity and loss of β -cell function were related to the need for insulin therapy [8]. However, to date, the treatment in patients with LADA has not been established: the clinical effectiveness of early introduction of insulin therapy for them is still controversial [2].

FRG is characterized by abnormal urinary glucose excretion in the absence of hyperglycemia [3]. It is a rare disease caused by an isolated renal tubular disorder, not accompanied by other proximal tubular transport abnormalities and renal dysfunction [3]. Therefore, patients with FRG are generally asymptomatic, and do not need medical intervention. The *SLC5A2* mutation has been confirmed to be responsible for the large majority of FRG, which explains the mechanism of FRG as a result from a defect in SGLT2 [9]. Although the *SLC5A2* mutation (c.875G > A, p.Cys292Tyr) in the present case has not been reported in patients with FRG, it was assessed as probably damaging with a score of 0.998 (sensitivity: 0.27; specificity: 0.99) by an *in silico* analysis.

Fortunately, our patient had never suffered from diabetic coma and showed improvement in HbA1c only with diet therapy, despite decreased insulin secretion. Considering that it has been recently reported that SGLT2 inhibitors have a positive effect on pancreatic β -cell function and glycemic control even in patients with type 1 diabetes as well as type 2 diabetes [10] [11], we assumed that SGLT2 inhibition might have some effective role for his clinical course. Further clinical and pathological studies are needed to clarify this effectiveness.

4. Conclusion

We experienced a novel case of LADA complicated by persistent isolated glucosuria in the absence of hyperglycemia. Our case clearly implies the clinical effectiveness of SGLT2 inhibition in patients with LADA.

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Right Inguinal Varicose Vein in Connection with Femoral Vein Following Intravenous Drug Abuse: A Rare Radiologic Finding

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Abstract

Varicose veins are enlarged, protuberant superficial veins that are palpable beneath the skin. The causes of such a venous pathology may be primary, secondary, or congenital. The major agents leading to the development of varicose veins include: Hereditary, prolonged standing, Increasing age, Heavy lifting, Prior superficial or deep vein clots, Female gender and Multiple pregnancies. In this manuscript, we report a case of inguinal varicose vein in connection with femoral vein, resulted from direct intravenous injection of drug. The diagnosis was made based on Doppler sonography.

Keywords

Substance Abuse, Intravenous, Varicose Vein

1. Introduction

Varicose veins are twisted, gnarled and swollen veins which are usually seen in lower extremities [1]. These are more common in women than men [2]. Some associated risk factors and causes are: obesity, pregnancy, menopause, aging, prolonged standing and leg injury. Some other factors also exist that are less pervasive like the direct intravenous injection [3] [4]. Intravenous drug abuse usually performs by drug users in the upper and lower extremities. Direct intravenous injection can have side effects which many of such cases have been reported so far. These include: infection, aneurysm, vascular necrosis and deep vein thrombosis. Based upon the radiologic texts, the present complication has relatively low incidence in general population and is valuable to be presented as a case report.

2. Case Presentation

A 26-year-old male referred to the clinical center with a bulging and pain in right inguinal area (**Figure 1**). The sociodemographic and clinical characteristics of this patient are shown in **Table 1**. He has had a history of substance abuse intravenously in his femoral vein two years ago. He noted that he had not been injected in this area from two years ago. No special past medical history such as: local or systemic infection, chronic non-communicable diseases existed. On examination, the patient was not febrile. Vital signs were normal. In the physical examination, no lymphadenopathy was detected. The femoral, popliteal, and distal pulses were touched. Vascular packets with extension to the groin as well

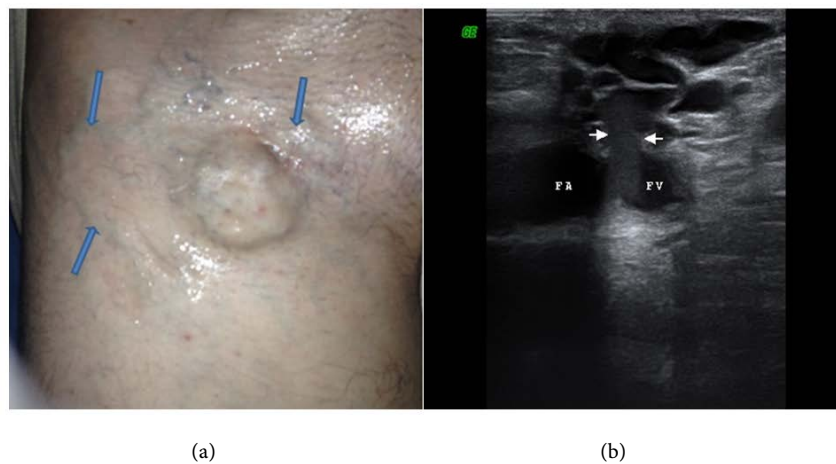


Figure 1. (a) Right inguinal demonstrates focal superficial protrusion, note prominent superficial veins at the periphery of the main lesion (arrows), (b) B-mode ultrasound image from focal inguinal bulging demonstrates injection site (between arrows) connected femoral vein and varicose packets, FA (femoral artery), FV (femoral vein).

Table 1. Sociodemographic and clinical characteristics of the patient.

Age (years)	26	Side of vein involvement	Right side
Marital status	Divorced	Risk factors	Smoking, local injection
Monthly family income	Less than 200 \$	Conservative management	Limb elevation, Compression stockings
Occupational status	Unskilled	Medical management	Analgesics, Oral anticoagulants
Education	illiterate	Surgical procedures	Saphenous vein stripping
Place of residence	Rural		
Signs	Inguinal swelling, vascular packets		
Symptoms	Right inguinal area bulging and pain		

as prominent vessels around the mass were observed. The blood flows distributed from the femoral vein into the packets following Valsalva maneuver, and the direct connection with femoral vein was obvious. Doppler ultrasonographic evaluation conducted to assess the exact blood flow patterns and the existed connection between the femoral vein and varicose packets. Changes in blood flow after Valsalva maneuver was also represented in **Figure 2**. The patient was followed for treatment. At first, the patient underwent conservative management and then medical and surgical.

3. Discussion

The leading causative agent of varicose veins is unknown. It involves about sixty percent of the general population in the modern countries with further epidemiologic prevalence in women [5]. Here in the present paper, we report a case of 26-year-old male with varicose vein secondary to direct intravenous drug abuse diagnosed by duplex ultrasound.

The mechanisms of varicosity are not obviously clarified. Reflux and incompetency occurring in the vein valves, and also dilation of the vein wall are primarily lead to venous varicosity [6]. Once the vessel wall escalating tensions happen, the expression/activity of matrix metalloproteinases (MMP) are also increasing [7]. Endothelial cell damage causes a cascade of leukocyte infiltration and inflammation, leading to more vein wall injury. In addition to the common risk factor for the disease like: prolonged standing, superficial or deep vein clots, female gender, multiple pregnancies, increasing age and heavy lifting; there are some other various factors that cause such disorders with mentioned mechanisms. Unusual etiologies of varicose veins in the lower extremities was evaluated in study conducted by Seung Chai Jung *et al.* [8]. They reported that the major rare factor of developing varicose vein was vulvoperineal varicosity, fol-

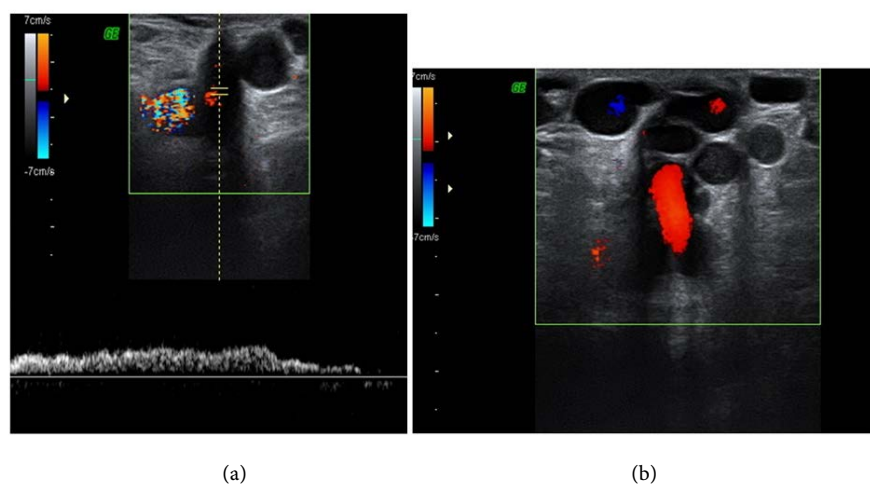


Figure 2. (a) Duplex ultrasound image after Valsalva at injection site demonstrates venous Doppler pattern; (b) Color Doppler ultrasound images after Valsalva maneuver from injection site demonstrates deep to superficial direction of flow, note engorged varicose packets also.

lowed by round ligament varicosity, persistent sciatic vein incompetence, intraosseous perforating vein incompetence, Klippel-Trenaunay syndrome, congenital venous malformation, and portosystemic collateral-related varicose vein. In our study, the varicose vein packets developed following direct intravenous injecting in the femoral vein. Senbanjo *et al.* examined the types of drug used to inject in the groin and its local consequences and complications. They concluded that heroin was the most common drug with was abused and deep vein thrombosis was the most prevalent complication [9]. The diagnosis of the disease is not so difficult but the etiologic factor is important and always is questionable. Diagnosis is often delayed and patients are not managed precisely for long period of time.

4. Conclusion

This case report establishes new horizon for clinicians in order to consider more probable etiologic factors for venous disorders. Such unusual cases may be detected with the combined modalities of CT venography and Duplex sonography.

Conflict of Interest Statement

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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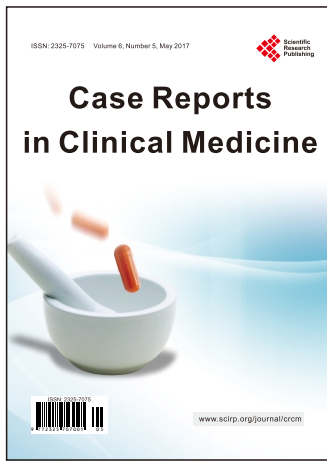
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