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Commentary
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Systemic Amyloidosis in a Patient with Type 2 Diabetes Mellitus as a Uncommon Cause of Non-Diabetic Renal Disease

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Abstract

Background: The incidence of non-diabetic renal disease is very high in type 2 diabetic patients. Systemic amyloidosis as one of the non-diabetic renal disease rarely occur in type 2 diabetes mellitus subjects and may have the high risk of early mortality.

Case report and management: We report a case in a 66-year-old patient with legs edema, inappetence and frothy urine for 2 weeks. The patient was diagnosed type 2 diabetes on routine testing 10 years ago without any symptoms. The blood glucose was adequately controlled with diet and exercise. Physical examination showed edema of lower extremities and hepatomegaly. 24 hrs urinary protein was 4.7 g. Blood investigation showed slightly impaired liver function while other results incluing serological studies and bone marrow aspirate showed negative or in normal range. Funduscopy showed normal retinal blood vessels and optic disc. Echocardiography revealed cardiac amyloidosis with septal hypertrophy and the ultrasound scan revealed hepatomegaly. Hepatic biopsy was performed and diagnosis of systemic amyloidosis was made due to positive congo red staining.

Conclusions: When massive proteinuria occurred in patient with type 2 diabetes and other internal organs like liver and heart are affected, superimposed systemic amyloidosis should be considered in particular.

Keywords: Non-diabetic renal disease; Primary systemic amyloidosis; Type 2 diabetes mellitus; Hepatic biopsy

Abbreviations: DN: Diabetic nephropathy; NDRD: Non-diabetic Renal Disease; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T2DM; Type 2 Diabetes Mellitus

Introduction

It is estimated that about 20%-40% of patients with type 1 or type 2 diabetes will develop diabetic nephropathy (DN), which contributes to most end-stage renal disease worldwide [1,2]. Diagnosis of DN is mostly clinically based on a long history of diabetes, proteinuria, hypertension, and a progressive decline in renal function. This diagnostic approach is inconclusive, due to the fact that non-diabetic renal disease (NDRD) has been found in type 2 diabetes mellitus (T2DM) patients. The prevalence of NDRD in type 2 diabetic patients with renal involvement varies from 20-80% [3-6]. The diagnose of NDRD in diabetic patients has an obvious prognostic and therapeutic importance. The common NDRD includes glomerulonephritides, vascular nephropathy, cholesterol microembolism and so on. Systemic amyloidosis is a rare disease with an incidence of 4.5 per 100000 person-years [7]. The pathological production of fibrillar proteins can deposit in numerous tissues and cause organ dysfunction including kidney, liver, heart, lung, spleen, gastrointestinal tract and bladder. Here, we describe a rare case of type 2 diabetes presenting with massive proteinuria due to primary systemic amyloidosis.

Case Presentation

A 66-year-old male was admitted on March 2014, presenting with edema of legs, in appetence and frothy urine for 2 weeks. He was diagnosed type 2 diabetes on routine testing 10 years ago without any symptoms. The diagnosis was based on the fasting glucose which shown 7.0 mmol/L and 7.1 mmol/L respectively on two occasions. The blood glucose was adequately controlled with diet and exercise for the first few years with HbA1c around 6.5%. However, in the last 4 years, he did not have any self-monitoring or go for a routine clinical consultation. The most recent fasting glucose was 10.8 mmol/L. There was no history of diabetic retinopathy or neuropathy. He denied family history of diabetes or systemic disease. His vitals displayed blood pressure of 107/66 mmHg. Pulse rate was 64/minute. His liver was palpable by 5 cm below the right costal margin. The rest of physical examination showed mild edema of lower extremities. Laboratory investigation revealed hemoglobin 117 g/L, serum creatinine 101 μmol/L, albumin 30.6 g/L, fasting blood glucose 9.6 mmol/L, uric acid 550 μmol/L. Urinalysis showed no dysmorphic erythrocytes, cellular casts, or crystals with 24 hrs urinary protein of 4.7 g. Quantitative immunoglobulins and serological studies including anti-nuclear antibody, anti-dsDNA, anti-neutrophil cytoplasmic antibody, anti-gluomerular basement antibodies, complement levels (C3,C4) and HIV, HBsAg, Anti HCV, Anti-CMV antibodies were all within the reference ranges. The synthetic liver function impaired slightly, such as alanine aminotransferase (ALT) at 132 IU/L, aspartate aminotransferase (AST) with TBIL 28.2 μmol/L (Table 1). Until now, the clinical diagnosis of nephrotic syndrome was made. However, whether the nephrotic syndrome was associated with type 2 diabetes was doubtful. Urine immunofixation found free λ Bence-Jones protein.

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Data	Result	Normal range	Data	Result
hemoglobin	117 g/L	120 - 160	**occult blood (urine)**	(-)
creatinine	101μmol/L	53 - 115	**sugar (urine)**	(-)
albumin	30.6 g/L	35.0 - 50.0	**protein (urine)**	3+
TP	55.0 g/L	64.0 - 87.0	**granular casts (urine)**	(-)
globulin	22.3 g/L	20.0 - 32.0	**urinary protein**	4.7 g/24 hrs
FBG Uric acid	9.6 mmol/L 550 μmol/L	2.9 - 6.0 200-430	**HbA1c** **ESR**	6.2% 9 mm/h
TG	9.41 mmol/L	0.33 - 1.70	**ANCA**	(-)
IgA	2.90 g/L	1.45 - 3.45	**ANA**	(-)
IgM	0.46 g/L	0.92 - 2.04	**ds-DNA**	(-)
IgG	6.63 g/L	10.13 - 15.13	**HIV antibody**	(-)
SAA	109 mg/L	1.00 - 6.40	**HbsAg**	(-)
C3	0.91 g/L	0.79 - 1.17	**HCV antibody**	(-)
C4	0.24 g/L	0.17 - 0.31	**Anti-GBM antibody**	(-)
ALT	161 U/L	1 - 40	**CMV antibo**dy	(-)
AST	132 U/L	1 - 37	**Urine immunofixation**	Bence-Jones
LDH	282 U/L	114 -240		protein free λ
TBIL	28.2 μmol/L	3.0 - 22.0	**Serum protein**	(-)
ProBNP	837.9 pg/mL	<84	**electrophoresis**	

Abbreviations: TP: total protein; FBG: fasting blood glucose; SAA: serum amyloid A; TG: triglyceride; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; TBIL: Total Bilirubin; HbA1c: Hemoglobin A1c; ESR: Erythrocyte Sedimentation Rate; ANCA: Myeloperoxidase Anti-neutrophil Cytoplasmic Antibodies; ANA: Anti nuclear Antibody; HCV: Hepatitis C Virus; CMV: Cytomegalovirus; GBM: Glomerular Basement Membrane

Table 1: Laboratory Data on Admission.

Serum protein electrophoresis revealed no evidence of monoclonal proteins. To exclude multiple myeloma, a bone marrow aspirate was performed. The plasma cells were found at 4% with typically 96.6% of CD56, 8.5% of κ, 91.5% of λ by flow cytometry.

Normal retinal blood vessels and optic disc were observed under funduscopy suggesting the absence of retinopathy. Electrocardiogram showed frequent multifocal ventricular premature beats and low voltage. Echocardiography revealed septal hypertrophy (13 mm) and thickening of left ventricular and right ventricular posterior wall (left ventricular posterior wall was 13 mm). It also showed expansion of both atriums (left atrial diameter: 40 mm, right atrial diameter: 62 mm×43 mm) with un-even enhanced myocardial echo. The cardiac valves were normal and LVEF was 60%. A small area of pericardial effusion was found. Ultrasound showed hepatomegaly (the diameter of right lobe was 22 cm) with homogeneous echo. Percutaneous hepatic biopsy was performed for diagnosis which revealed amyloid deposits in hepatic sinusoids with positive Congo red staining and kappa (-), lambda (-), CD56 (-). So far systemic amyloidosis was diagnosed. The patient refused further chemotherapy and started to treat with sitagliptin (100 mg/day) along with losartan (50 mg/day). Interestingly, he suffered orthostatic hypotension with a fall blood pressure at 80/50 mmHg after an upright position while the supine blood pressure at 110/70 mmHg. So, he stopped taking the losartan. Six months after the initial diagnosis, the patient was still alive but presented with poor condition.

Discussion

Diabetic nephropathy is a complication of diabetes associated with the kidney which could progressively lead to end-stage renal diseases [2]. The diagnosis of DN is frequently based on clinical characterization exclusively. Actually, a variety of NDRDs are often overlooked in diabetic patients, which have significant impacts on prognosis and treatment. The challenges still exist to differentiate NDRD from DN in diabetic patients. Therefore, renal biopsy is the only tool to diagnose NDRD. However, the renal biopsy cannot be used as a routine diagnostic test in type 2 diabetic patients with proteinuria because of the invasiveness. Therefore, the main indication for renal biopsy was clinically thorough suspicion of NDRD. The common indications for NDRD in type 2 diabetes are short duration of type 2 diabetes, acute or rapidly progressive renal failure, glomerular hematuria, absence of diabetic retinopathy, nephritic syndrome with normal renal function [3,8,9]. As in our case, despite the patients having T2DM for more than 10 years, high level of proteinuria without retinopathy suggests a diagnosis of NDRD other than DN. Thus, biopsy was considered in our patient for the precise diagnosis.

A wide spectrum of NDRNs reported in patients with type 2 diabetes mainly include glomerular and tubulointestinal lesions [10-12]. In our case, we diagnosed the systemic amyloidosis which is an infrequent cause of non-diabetic renal disease in patient with type 2 diabetes based on positive Congo red staining. Systemic amyloidosis is a rare and severe disease which involves several organs including kidney, liver, heart, lung, spleen, gastrointestinal tract, bladder and endocrine system and leads to a high motality rate [13,14]. Without treatment, the median survival is less than 6 months [15]. For all newly diagnosed cases of amyloidosis, an assessment of the specific type of amyloid is critical in ensuring proper therapy. In our case, free λ Bence-Jones protein was found in urine immunofixation. But the histochemical staining revealed negative kappa and lambda. Thus, the type of amyloid is needed further confirmed by using polymerase chain reaction amplification and sequencing of mutated genes. Based on the examination, our patient presented with multiorgan affected like liver and heart. Renal disease as a frequent manifestation of the systemic amyloidosis usually cause proteinuric renal failure in the context of normal or low blood pressure. Interestingly, despite taking the small dose of losartan, our patient had developed orthostatic hypotension. It is indicated that autonomic nervous may be affected. Prognosis is determined by the number and severity of involved internal organ, the heart involvement in particular [16]. Left atrial enlargement is proved as an independent predictor of total long-term survival [17].

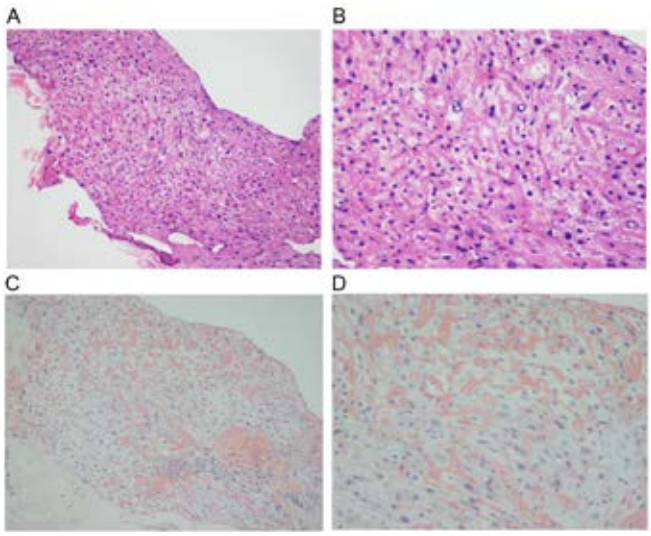

Figure 1: A liver-biopsy specimen stained with Hematoxylin and eosin ×200 (A); ×400 (B) shows a eosinophilic amorphous material deposits in hepatic sinus. The Congo staining reveals amyloid deposits in the hepatic sinus ×200(C); ×400(D).

In our case, echocardiography showed expansion of both atrium and left ventricle with enhanced myocardial echo which strongly suggested the cardiac amyloidosis. Base on the multiorgan involvement with laboratory measurements and additional examination especially the cardiac parameter, we identify that our patient with highest risk of early mortality (Figure 1).

Conclusion

When a patient of type 2 diabetes presents proteinuria and exhibits several organs involvement like liver and heart, systemic amyloidosis should be considered rather than diabetic nephropathy.

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