

## Case Report

# Diabetic Nephropathy Simulating Autoimmune- Related Glomerulonephritis: A Case Report

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### Abstract

**Background:** In patients with type 2 diabetes mellitus, physiological autoimmunity is seemingly activated by chronic inflammation primarily because of blood sugar deposition, resulting in biological tissue destruction; this triggers the release of abnormal signals from injured cells that successively trigger an autoimmune response by activating the innate and adaptive immune systems. In addition, diabetic patients might present with some features of autoimmune disease.

**Case presentation:** Herein, we report the case of a 67-year-old female with diabetes mellitus presenting with generalized edema, rapidly deteriorating renal function, nephrotic-range proteinuria, and high-titer antinuclear antibody. The initial diagnosis of autoimmune disease-induced rapidly progressive glomerulonephritis was substantial; however, the following renal pathology revealed advanced diabetic nephropathy with interstitial fibrosis. No immunosuppressants but maintenance hemodialysis was prescribed for her.

**Conclusion:** Therefore, we present an interesting case of diabetic nephropathy, which presented the clinical feature of autoimmune-related glomerulonephritis. Renal biopsy suggested as clinical guideline should be performed without hesitation when facing such condition.

**Keywords:** Acute renal failure; Autoimmune nephropathy; Diabetes mellitus; Proteinuria; Renal biopsy

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### List of Abbreviations

DM: Diabetes mellitus

HbA1C: Glycated hemoglobin

RPGN: Rapidly progressive glomerulonephritis

ANA: Antinuclear antibody

Ig: Immunoglobulin

C: Complement

### Background

Various types of nephropathies involved in immunological mechanism are often manifested with the acute onset of hematuria, proteinuria, hypertension, edema, and reduced renal function. Pathologically, the deposition of antibodies or immune complexes in the glomerulus results in inflammation, damage, and destruction of renal cells [1]. In addition, the classic presentation of diabetic nephropathy overlaps with proteinuria, reduced glomerular filtration rate, and elevated blood pressure compared with that of autoimmune nephropathy. Previously, the auto immune response in diabetic nephropathy is investigated in types 1 and 2 Diabetes Mellitus (DM), including cytokines and chemokines secretion and the activation of macrophages, complements, and lymphocytes, all involved in the pathological course [2]. Thus, rarely the symptomatic clinical features are not precisely differentiated between diabetic and autoimmune nephropathies.

Herein, we present a rare case of a patient with diabetic nephropathy who was accurately diagnosed with a renal biopsy but initially indicated the presence of autoimmune nephropathy. Such unique course and presentation piqued our interest and suspicion of the traditional practice of the necessity of renal biopsy for diabetic nephropathy.

### Case Presentation

A 67-year-old Taiwanese female with a history of type 2 DM for >15 years with peripheral and diabetic retinopathies after laser photocoagulation was undergoing regular medical treatment, including long-acting insulin and oral hypoglycemic agents, at a regional hospital. Before 2016, her glycated hemoglobin (HbA1C) level was 8%-10%, which improved to 6%-7% after mid-2016. Within three months, she developed generalized edema and rapidly deteriorating renal function, following which she was referred to our hospital. Peripheral edema developed almost three months prior and worsened in the past three weeks. The patient denied the symptoms of recent fever, sore throat, arthralgia, swollen joints, dark urine, or visible hematuria. Furthermore, she presented no skin rash, mucosal ulcerations, hair loss, the shortness of breath, cough, hemoptysis, or neuropsychiatric symptoms. However, the decline in the urine output was apparent in the last two weeks.

Upon admission, her physical examination findings were as follows: elevated blood pressure, 180/78mmHg; body temperature, 35.2°C, heart rate, 81 beats/min without a murmur; and respiratory

rate, 17/min without lung crackles. In addition, the examination of her head and neck was normal without facial rash, periorbital edema, lymphadenopathy, thyroid enlargement, or mucosal ulcerations. Table 1 summarizes the initial laboratory data upon admission. The primary findings of serum chemistries included impaired renal function (creatinine, 7.3mg/dL and baseline creatinine, 2.7mg/dL prior to 6 months) and hypoalbuminemia (albumin, 2.6gm/dL). In addition, urinalysis revealed hematuria and nephrotic-range proteinuria (urine protein and creatinine ratio, 36.3). Subsequently, renal ultrasonography revealed no hydronephrosis, and bilateral kidneys were within the normal size (right, 9.4cm; left, 9.65cm) but had increased echogenicity.

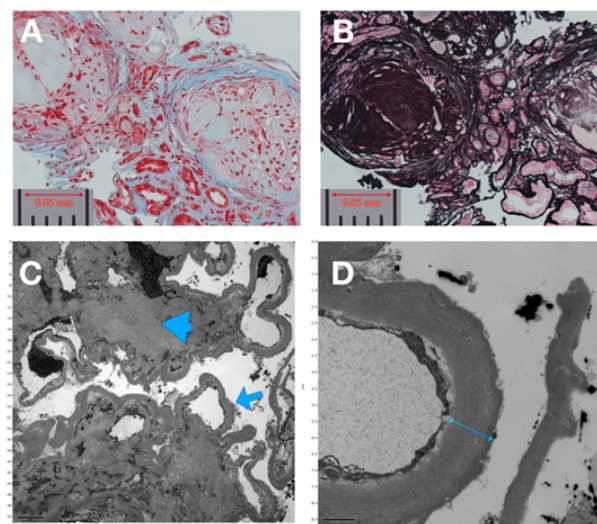
	Results	Reference Range
<b>Blood Chemistries</b>		
BUN (mg/dL)	117	Jul-25
Creatinine (mg/dL)	7.3	0.5-1.3
Uric Acid (mg/dL)	7.3	2.3-6.6
Sodium (meq/L)	119	133-145
Potassium (meq/L)	4.6	3.3-5.1
Chloride (meq/L)	90	96-108
Calcium (mg/dL)	3.83	3.68-5.6
Total Cholesterol (mg/dL)	184	0-200
Triglyceride (mg/dL)	253	0-150
Albumin (gm/dL)	2.6	3.5-5.7
Albumin/globulin	1.3	1.1-2.2
HbA1C (%)	6.6	3.5-5.5
Hemoglobin (gm/dl)	6.2	Nov-16
MCV (fl)	82.6	81-98
<b>Autoimmunity Survey</b>		
IgG (mg/dL)	361	751-1560
IgA (mg/dL)	193	82-453
IgM (mg/dL)	19.1	46-304
C3 (mg/dL)	62.2	79-152
C4 (mg/dL)	18.4	16-38
ANA (IFA)	640x+CEN	Negative
BM zone Ab	20x-	Negative
MPO ANCA (IU/mL)	<0.2	<3.5
PR3 ANCA (IU/mL)	<0.2	<2
Anti-cardiolipin IgG (GPL)	<0.5	0-40
Anti-ds DNA (IU/mL)	<0.5	0-15
Anti-β2glucoprotein (U/mL)	<0.6	0-10

**Table 1:** Laboratory data at admission.

**Note:** Abbreviation: BUN: Blood urea nitrogen; HbA1C: Glycated hemoglobin; MCV: Mean Corpuscular Volume; Ig: Immunoglobulin; C: Complement; ANA: Antinuclear Antibodies; CEN: Centromere; BM zone Ab: Basement Membrane Zone antibody; MPO ANCA: Myeloperoxidase-antineutrophil Cytoplasmic Antibody; PR3 ANCA: Proteinase 3 anti-neutrophil Cytoplasmic Antibody; Anti-ds DNA: Anti-double stranded deoxyribonucleic acid; Anti-β2 glucoprotein: Anti-Beta2 Glycoprotein.

Initially, the diagnosis of Rapidly Progressive Glomerulonephritis (RPGN) was impressed. The following autoimmune antibody test was positive for antinuclear antibody (ANA-640x+centromere pattern) but other serological test results were all negative

(Table 1). Lastly, we performed a renal biopsy to establish the diagnosis of RPGN. However, light microscopy revealed no glomerular crescentic formation, but revealed diffuse nodular glomerulosclerosis with mesangial matrix expansion and advanced interstitial fibrosis (Figure 1(A-B)). Electron microscopy revealed a thickened glomerular basement membrane and the effacement of podocyte foot processes (Figure 1(C-D)). Furthermore, although immunofluorescence examination was negative in immunoglobulin (Ig)A, IgM, complement (C)1q, and C3, it displayed pseudolinear staining of IgG.



**Figure 1:** Renal pathology (A) Masson trichrome stain shows advanced interstitial fibrosis (>60%), (B) silver stain shows sclerotic nodules with a lamellated appearance in light microscopy; (C) the effacement of podocyte foot processes with microvillous transformation and pleomorphic changes (arrow) and the expansion of mesangial matrix (arrowhead), and (D) Glomerular Basement Membrane (GBM) thickness was 1388nm (double arrow) in electron microscopy.

Based on Clinicopathological correlations, the patient was diagnosed with advanced diabetic nephropathy and diffuse glomerulosclerosis. We prescribed no immunotherapy and, subsequently, scheduled regular hemodialysis because of the irreversible renal damage.

## Discussion

Diabetic nephropathy is arguably the major cause of chronic renal failure, necessitating dialysis in the developed world [3]. Type 1 DM is an autoimmune disease caused by the autoimmune response against pancreatic β-cells [4]. However, type 2 DM has long been viewed as the chronic inflammatory state. Currently, the stereotypical concept that type 2 DM exclusively is a metabolic disease has been altered by determining the overlapping characteristics of inflammation and autoimmunity [2]. In addition, innate and adaptive immune systems, including T cells, macrophages, dendritic cells, and circulating auto antibodies, have been reported to contribute to the inflammation, damage, and acceleration of diabetic nephropathy [3]. At the molecular level, a wide array of inflammatory molecules, including transcription factors, cytokines, chemokines, adhesion molecules, and nuclear receptors, are involved in the pathological development of diabetic nephropathy [5,6].

Although the diagnosis of diabetic nephropathy is primarily dependent on clinical presentations, particularly the detection of microalbuminuria, the necessity of performing a renal biopsy for diabetic

patients who developed the symptoms of glomerular diseases, is debatable [7]. In type 1 DM, diabetic nephropathy typically develops 10 years after the onset; however, this term is variable in type 2 DM [8,9]. At present, renal biopsy is recommended for diabetic patients suspected of nephropathies other than diabetic nephropathy [10], including the rapid onset of proteinuria, absence of retinopathy, presence of hematuria, active urinary sediment, and rapid decline in renal function [11,12].

A pathological hallmark of human diabetic nephropathy is a nodular lesion, often known as a Kimmelstiel-Wilson lesion, characterized by the accretion of homogeneous eosinophilic material within the mesangium and often appears as a round accentuation of the mesangial expansion [13]. A study proposed that two processes play crucial roles in the formation of nodular lesions; the first is the detachment of endothelial cells from the glomerular basement membrane, and the second is mesangiolysis [14]. However, another study reported that the major findings of autoimmune-related glomerulonephritis include positive immunofluorescence and immunoglobulin deposition [15]. In addition, pauci-immune glomerulonephritis was shown to present negative immunofluorescence but crescentic formation in the glomerulus [16].

Patients with diabetic nephropathy rarely present a variety of autoantibodies [17], owing to the reasons mentioned earlier, mimicking autoimmune-related glomerulonephritis. Thus, determining the real etiology in such settings is imperative because the treatment policy of diabetic nephropathy and autoimmune-related glomerulonephritis varies considerably. In fact, immunotherapy might be required for autoimmune-related glomerulonephritis to preserve normal renal function, but it is not required for diabetic nephropathy. In our case, the patient presented with initial clinical symptoms of generalized edema, proteinuria, hematuria, and positive ANA, all compatible with "RPGN because of autoimmune disease." However, the findings of kidney pathology revealed advanced diabetic nephropathy. Thus, we hypothesized that the positive ANA could result from DM. Hence, we prescribed the patient no more immunotherapy.

## Conclusion

This report presents a compelling case of diabetic nephropathy that expressed the clinical features of autoimmune-related nephropathy. The findings of our case highlight the necessity of performing a renal biopsy prior to initiating immunosuppressant therapy in patients with DM presenting with acute glomerulonephritis.

## Declaration

**Ethics approval and consent to participate:** Ethic approval was waived by the ethics committee at the Shin Kong Wu Ho-Su Memorial Hospital because our case study was based on chart review.

**Consent for publication:** Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

**Availability of data and materials:** Not applicable.

**Competing interests:** The authors declare that they have no competing interests.

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**Author's contribution:** PLP performed the clinical assessments and drafted the manuscript and table and was the major contributor in writing the manuscript. MHT and YWF performed the clinical assessments and assisted in drafting the manuscript. AHY provided the documentation about the pathological finding of kidney in our case. MHT was responsible for clinical care of the patient. MHT and YWF co-reviewed and revised the manuscript critically for intellectual content. All authors read and approved the final manuscript.

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