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Diagnostic Utility of Direct Immunofluorescence in Non-Diabetic Kidney Diseases Among Type II Diabetic Patients

[1]Dr. Aayushi Singhal, Department of Pathology, MGM Institute of Health Sciences, Kamothe, Panvel, Navi Mumbai, Maharashtra - 410206, India.

[2]Dr. Sunil Deshpande MD (Pathology), Consultant Nephropathologist, Department of Pathology, Deshpande Pathology Laboratory and Immunofluorescence Centre, 4th floor, Clover centre, Camp, Pune - 411001, Maharashtra, India.

[3]Dr. Ujwala Maheshwari, MD (Pathology), Professor, Department of Pathology, MGM Institute of Health Sciences, Kamothe, Panvel, Navi Mumbai, Maharashtra - 410206, India.

Corresponding Author: Dr. Ujwala Maheshwari, MD (Pathology), Professor, Department of Pathology, MGM Institute of Health Sciences, Kamothe, Panvel, Navi Mumbai, Maharashtra - 410206, India.

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Abstract

Background: Diabetic Nephropathy (DN) is the leading cause of end-stage kidney disease (ESKD) globally and a major microvascular complication of diabetes. However, Non-Diabetic Kidney Disease (NDKD), including glomerular (e.g., membranous nephropathy, IgAnephropathy), tubulointerstitial, and vascular diseases, either in isolation or in combination with Diabetic Nephropathy (DN) in patients with diabetes. Recent reports indicate an increasing prevalence of NDKD in diabetics, likely due to aging, infections, monoclonal gammopathies, and malignancies. Timely diagnosis of NDKD is critical, as early treatment may halt, reverse, or significantly slow progression to CKD or ESKD. Type 2 DM patients are more commonly affected by NDKD than those with Type 1 DM. While clinical and biochemical parameters may raise suspicion for NDKD, kidney biopsy with Direct Immunofluorescence (DIF) remains the gold standard for distinguishing DN from NDKD. DIF plays a crucial role in identifying immune-complex mediated glomerulopathies that might be missed on light microscopy alone, guiding therapeutic decisions and influencing prognosis. Accurate biopsy interpretation demands thorough understanding of renal pathology, correlating clinical, laboratory, light microscopy, and immunofluorescence findings.

Aim: To study the histopathological spectrum of non-diabetic kidney diseases (NDKD) in patients with Type II Diabetes Mellitus using immunofluorescence, and to correlate the clinical presentation and laboratory findings with the histopathological diagnosis.

Study Design: A prospective, observational study conducted over 1.5 years (January 2023–June 2024) at MGM Medical College and Hospital, Navi Mumbai. The study included 50 ultrasound-guided renal biopsies from patients diagnosed with Type II Diabetes Mellitus, selected based on clinical suspicion of NDKD.

Result: A total of 50 cases were studied, comprising 19 cases of isolated NDRD, 17 cases of combined NDRD with Diabetic Nephropathy (NDRD+DN), and 14 cases of isolated Diabetic Nephropathy (DN). The peak incidence was observed in the 40–60-year age group. Of the 50 patients, 39 (78%) were males and 11 (22%) were females, yielding a male-to-female ratio of 3.5:1, indicating male predominance. A significant association was noted between longer duration of diabetes and higher HbA1c levels with cases of isolated DN. Among the NDRD and NDRD+DN groups, the most common histopathological lesions identified were Acute Tubular Injury (ATI) and Acute Pyelonephritis (APN), possibly reflecting changing epidemiological trends, increasing age, infections, and malignancy risk in this population. Direct Immunofluorescence (DIF) proved indispensable for diagnosing immune complex glomerulopathies. While Linear IgG deposits along the glomerular basement membrane confirmed DN, granular deposits of IgA, IgM, C3, and C1q were diagnostic of NDRD subtypes such as IgA Nephropathy, Membranoproliferative Glomerulonephritis (MPGN), and Post-Infectious Glomerulonephritis (PIGN).

Conclusion

It is imperative to evaluate diabetic patients—especially those with a shorter duration of diabetes or lower HbA1c—who present with sudden-onset proteinuria, an acute rise in serum creatinine, or atypical urinary findings. Early renal biopsy in such cases facilitates timely diagnosis and management of NDRD. Accurate histopathological diagnosis, supplemented by DIF, is crucial for initiating timely and specific treatment, which may prevent progression to chronic kidney disease or end-stage kidney disease. By enhancing diagnostic accuracy, DIF helps optimize clinical outcomes, prevents under diagnosis or misdiagnosis of NDRD, and underscores the need for its routine inclusion in renal biopsy analysis for diabetics with atypical presentations.

Keywords: Type II Diabetes Mellitus, Non-Diabetic Renal Disease, Diabetic Nephropathy, Renal Biopsy, Direct Immunofluorescence, Immune-Complex Glomerulonephritis, Acute Tubular Injury, Diagnostic Utility.

Introduction

Diabetic nephropathy (DN) remains the foremost cause of end-stage renal disease (ESRD) globally. However, it is increasingly recognized that a significant proportion of renal dysfunction in diabetic patients arises from non-diabetic renal diseases (NDRD). Differentiating DN from NDRD is essential, as many NDRDs are reversible with timely diagnosis and appropriate treatment. Direct Immunofluorescence (DIF) serves as an indispensable diagnostic modality to identify immune-complex-mediated glomerulopathies, which may otherwise be missed on routine histopathology alone. This study aimed to evaluate the prevalence and histopathological spectrum of NDRD in patients with Type II Diabetes

Mellitus (T2DM) and to highlight the pivotal role of DIF in establishing a definitive diagnosis.

Aim

To study the histopathological spectrum of non-diabetic kidney diseases (NDRD) in patients with Type II Diabetes Mellitus and to emphasize the diagnostic utility of Direct Immunofluorescence (DIF) in renal biopsies.

Material and Methods

A prospective, observational study was conducted over a period of 18 months (January 2023 to June 2024) at MGM Medical College and Hospital, Navi Mumbai. A total of 50 ultrasound-guided renal biopsies were performed on patients with T2DM who presented with clinical features suggestive of NDRD. Inclusion criteria comprised sudden onset nephrotic-range proteinuria, microscopic hematuria, rapid deterioration in renal function, absence of diabetic retinopathy, or refractory hypertension. Each patient underwent detailed clinical evaluation, laboratory investigations, histopathological examination using light microscopy (LM) and DIF analysis.

The renal biopsies were classified into three groups:

- Group I: Isolated NDRD
- Group II: Isolated DN
- Group III: Combined NDRD + DN

Clinical parameters analyzed included age, sex distribution, duration of diabetes, glycosylated haemoglobin (HbA1c) levels, serum creatinine, 24-hour urinary protein excretion, and blood pressure status.

Result

Out of 50 patients biopsied, 19 cases (38%) were diagnosed with isolated NDRD, 17 (34%) had NDRD superimposed on DN, and 14 (28%) showed isolated DN. The male predominance was evident (78%, M: F ratio of 3.5:1), and the peak incidence occurred in the 40–60 years age group.

Duration of diabetes and elevated HbA1c levels showed a significant association with isolated DN. Patients presenting with atypical features—shorter duration of diabetes, lower HbA1c, sudden-onset nephrotic syndrome, or hematuria—were more frequently diagnosed with isolated NDRD.

Acute Tubular Injury (ATI) and Acute Pyelonephritis (APN) were the most common histopathological findings in the isolated NDRD and combined NDRD+DN groups. Among isolated NDRD cases, Focal Segmental Glomerulosclerosis (FSGS) and Membranous Glomerulonephritis (MGN) pattern were also notable.

DIF proved indispensable in diagnosing immune-complex-mediated lesions. Linear IgG staining along glomerular basement membranes was a hallmark of isolated DN. In contrast, granular deposits of IgA, IgM, C3, and C1q were identified in cases of IgA nephropathy, Membranoproliferative Glomerulonephritis (MPGN) pattern, and Post-Infectious Glomerulonephritis (PIGN), primarily contributing to the NDRD group.

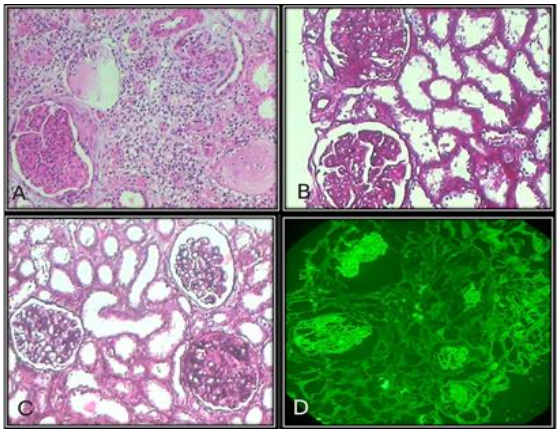

Figure 1: Acute Infection Related Glomerulonephritis with Acute Tubular Injury

A. Hematoxylin and Eosin Stain

B. Periodic Acid Schiff Stain
C. Jones Methenamine Silver Stain
D. Direct Immunofluorescence- C3 +++ deposits along GBM and mesangium

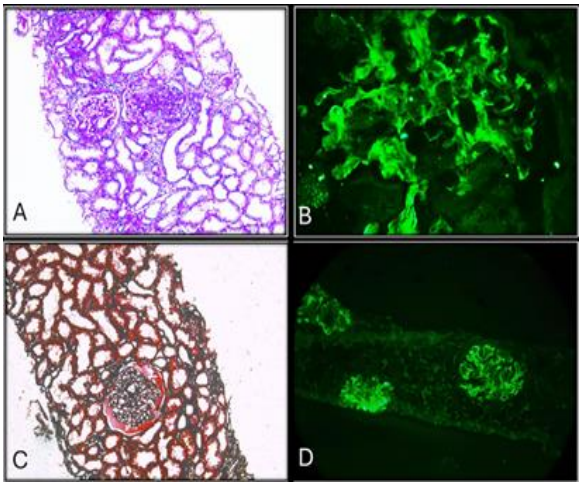

Figure 2: Ig A Nephropathy

A. Periodic Acid Schiff Stain- Pseudo-crescent in IgA nephropathy.
B. Direct Immunofluorescence- IgA ++ mesangial deposit.
C. Jones Methenamine Silver Stain- Pseudo-crescent in IgA nephropathy.
D. Direct Immunofluorescence- IgA ++ mesangial deposit

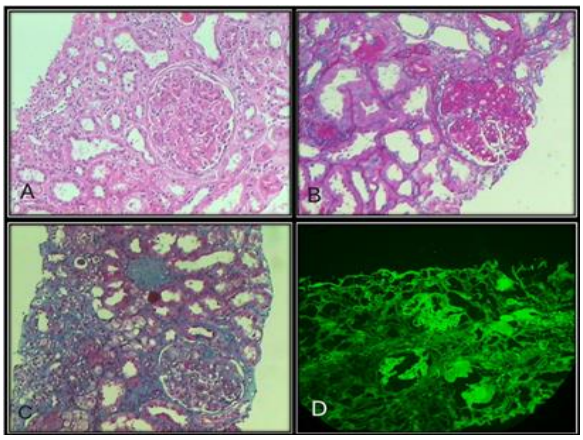

Figure 3: Membranoproliferative Glomerulonephritis

A. Hematoxylin and Eosin Stain
B. Periodic Acid Schiff Stain
C. Masson's Trichome Stain
D. Direct Immunofluorescence- C3 +++ GBM & mesangial deposit

Discussion

The findings of this study align with recent reports suggesting an increasing prevalence of NDRD in diabetic patients. This can be attributed to demographic transitions, increasing susceptibility to infections, polypharmacy, use of nephrotoxic drugs, malignancies, and monoclonal gammopathies in an aging diabetic population.

Several previous studies have highlighted the diagnostic dilemma in distinguishing DN from NDRD based on clinical grounds alone. While traditional clinical markers such as the presence of diabetic retinopathy or duration of diabetes have been employed to predict DN, these features are neither sensitive nor specific. Consequently, renal biopsy remains the gold standard for accurate diagnosis.

The role of DIF in renal biopsies is irrefutable. While light microscopy may demonstrate features suggestive of DN (such as mesangial expansion, nodular glomerulosclerosis, arteriolar hyalinosis, capsular drops, and fibrin caps), overlapping features with NDRD often necessitate immunopathological correlation. DIF bridges this gap by providing direct evidence of immune-complex deposition.

Linear IgG deposits, characteristic of DN, help confirm diagnosis in classical diabetic nephropathy. Conversely, granular immune deposits, especially of IgA or C3, immediately redirect the diagnosis towards immune-mediated glomerulopathies—conditions that may benefit from immunosuppressive therapy. This distinction is clinically meaningful, as failure to identify and appropriately treat NDRD may lead to unnecessary progression to ESRD despite optimal glycemic control.

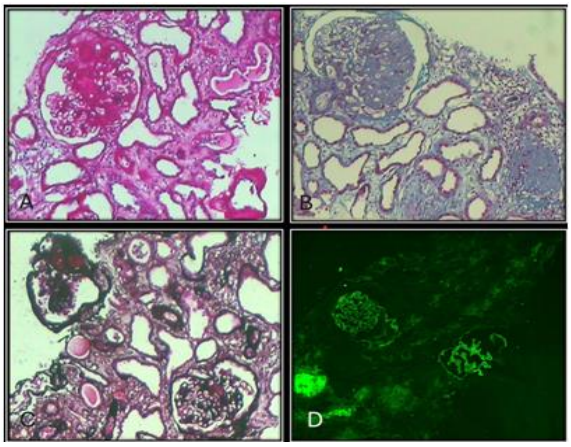

Figure 4: Diabetic Nephropathy

A. Periodic Acid Schiff Stain
B. Masson's Trichome Stain
C. Jones Methenamine Silver Stain
D. Direct Immunofluorescence- IgG ++ deposits along capillary/tubular basement membrane and Bowmann's capsule

The predominance of ATI and APN in NDRD in this study resonates with emerging data indicating a shift in the spectrum of NDRD from primarily glomerular diseases (like IgA nephropathy) to tubulointerstitial pathologies. Increasing life expectancy, recurrent urinary tract infections, indiscriminate use of antibiotics and analgesics, and poor glycemic control may all contribute to this trend.

Our study further reinforces the correlation between longer diabetes duration, higher HbA1c, and isolated DN, consistent with previously published meta-analyses. However, the presence of mixed lesions (NDRD+DN) underscores that even long-standing diabetic patients may harbour treatable renal conditions.

Expanded Analysis and Implications: A key takeaway from this study is the need to refine clinical suspicion thresholds for NDRD in diabetic patients. Traditionally, nephrologists may defer biopsy in long-standing diabetics, attributing renal dysfunction solely to DN. However, the presence of NDRD in over two-thirds of our biopsied diabetic patients indicates that a more liberal biopsy strategy might be warranted, especially in tertiary care settings with biopsy and DIF facilities.

Furthermore, DIF not only aids diagnosis but also stratifies prognosis. Immune-complex glomerulopathies typically carry variable prognoses depending on the underlying etiology and responsiveness to immunosuppression. For instance, IgA nephropathy and MPGN pattern, when diagnosed early, can be managed to slow or even reverse renal function decline.

Table 1: Prevalence of NDRD in the study group

Renal biopsy	Number of cases	%age of cases
Isolated DN	14	28%
NDRD+DN	17	34%
Isolated NDRD	19	38%
Total	50	100%

Table 2: Demographics across various groups

	Isolated DN (n=14)		NDRD+DN (n=17)		Isolated NDRD (n=19)	
Gender	No.	%age	No.	%age	No.	%age
Male	11	78.57	13	76.47	15	78.95
Female	3	21.43	4	23.53	4	21.05
Total	14	100	17	100	19	100
Age (years)	Mean	SD	Mean	SD	Mean	SD
	55.5	11.24	56.7	9.32	53.89	12.86

Table 3: Duration of Diabetes and HbA1c value

	Isolated DN (n=14)		NDRD+DN (n=17)		Isolated NDRD (n=19)	
	Mean	SD	Mean	SD	Mean	SD
Duration of Diabetes (years)	19.35	8.52	17.76	10.67	2.33	1.74
HbA1c Value	12.18	1.43	9.42	1.68	9.14	1.08

Table 4: Distribution of final diagnosis in different groups

Diagnosis	NDRD+DN (n=17)		Isolated NDRD (n=19)	
	No.	%age	No.	%age
IgA Nephropathy	0	0.0	2	10.53
Acute Tubular Injury/ Acute Pyelonephritis	7	41.18	6	31.58
Hypertensive Nephropathy	0	0.0	1	5.26
Focal Segmental Glomerulosclerosis(FSGS)	3	17.65	4	21.05
Acute Infection Related GN/ Acute Tubular Injury	3	17.56	1	5.26
Membranous Glomerulonephritis	0	0.0	3	15.79
Membranoproliferative Glomerulonephritis	2	11.76	1	5.26
Acute Tubular Injury with Acute Pyelonephritis	2	11.76	0	0.0
Chronic Glomerulonephritis with Tubulointerstitial Nephritis	0	0.0	1	5.26
Total	17	100.0	19	100.0

Clinical Implication

Given the increasing recognition of NDRD in diabetic patients, particularly those presenting atypically, routine DIF evaluation in renal biopsies should be advocated. By incorporating DIF into the diagnostic algorithm, nephrologists and pathologists can optimize patient care by initiating appropriate immunomodulatory or antimicrobial therapies early in the disease course, potentially halting or reversing renal deterioration.

Conclusion

Direct Immunofluorescence plays a crucial role in the accurate histopathological assessment of renal biopsies in T2DM patients. The utility of DIF extends beyond confirmation of DN to the precise identification of a wide array of reversible NDRDs. This study supports the routine inclusion of DIF in evaluating diabetic patients with atypical renal presentations to improve diagnostic accuracy and clinical outcomes.

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