

[CASE REPORT]

Fibronectin Glomerulopathy Confused with Glomerular Endothelial Injury in a Patient with Takotsubo Cardiomyopathy

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Abstract:

A 46-year-old woman developed takotsubo cardiomyopathy and nephrotic syndrome. The first kidney biopsy suggested non-immune-complex-mediated membranoproliferative glomerulonephritis (MPGN), and she was diagnosed with glomerular endothelial injury associated with takotsubo cardiomyopathy. A second biopsy was performed two years later because of persistent proteinuria despite renin-angiotensin system inhibition. This biopsy indicated non-immune-complex-mediated MPGN, but a mesangial and subendothelial substance of a higher electron density than that in the first biopsy was detected, suggesting the possibility of glomerular disease with non-immune deposits rather than endothelial injury. Finally, she was diagnosed with fibronectin nephropathy. Although rare, fibronectin glomerulopathy should be considered in non-immune-complex-mediated MPGN.

Key words: fibronectin glomerulopathy, takotsubo cardiomyopathy, endothelial injury, nephrotic syndrome

(Intern Med 61: 2027-2032, 2022)

(DOI: 10.2169/internalmedicine.8776-21)

Introduction

Fibronectin glomerulopathy is a rare, inherited, autosomal dominant kidney disease characterized by massive glomerular deposits of fibronectin and usually presents with mild to nephrotic-range proteinuria, hematuria, renal function impairment, and hypertension (1). This disease is usually diagnosed between the second and fifth decades of life (1, 2). Key histopathological features are a lobular appearance of the glomerulus with massive plasma-derived fibronectin deposits (3).

Takotsubo cardiomyopathy presents as a transient left ventricular dysfunction that mimics acute myocardial infarction (4). Approximately 10% to 20% of patients with takotsubo cardiomyopathy develop acute kidney injury (AKI) (5, 6). Although the pathogenesis of AKI in patients with takotsubo cardiomyopathy is not completely elucidated, hemodynamic instability plays an important role in AKI de-

velopment (4). To our knowledge, no secondary glomerular disease caused by, or associated with, takotsubo cardiomyopathy has been reported.

We herein report a patient who almost simultaneously developed takotsubo cardiomyopathy and nephrotic syndrome. The patient was initially diagnosed with a glomerular endothelial injury at least partly associated with takotsubo cardiomyopathy but was later diagnosed with fibronectin glomerulopathy.

Case Report

A 46-year-old woman presented with a paretic right arm. She had no notable personal medical history or family history of kidney disease, but a high blood pressure (144/91 mmHg), proteinuria, and an abnormal electrocardiogram (ST segment elevations) had been noted for the first time at her annual health checkup approximately 1 month earlier. Magnetic resonance imaging identified an early left cerebellar

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Received: October 4, 2021; Accepted: October 22, 2021; Advance Publication by J-STAGE: December 4, 2021

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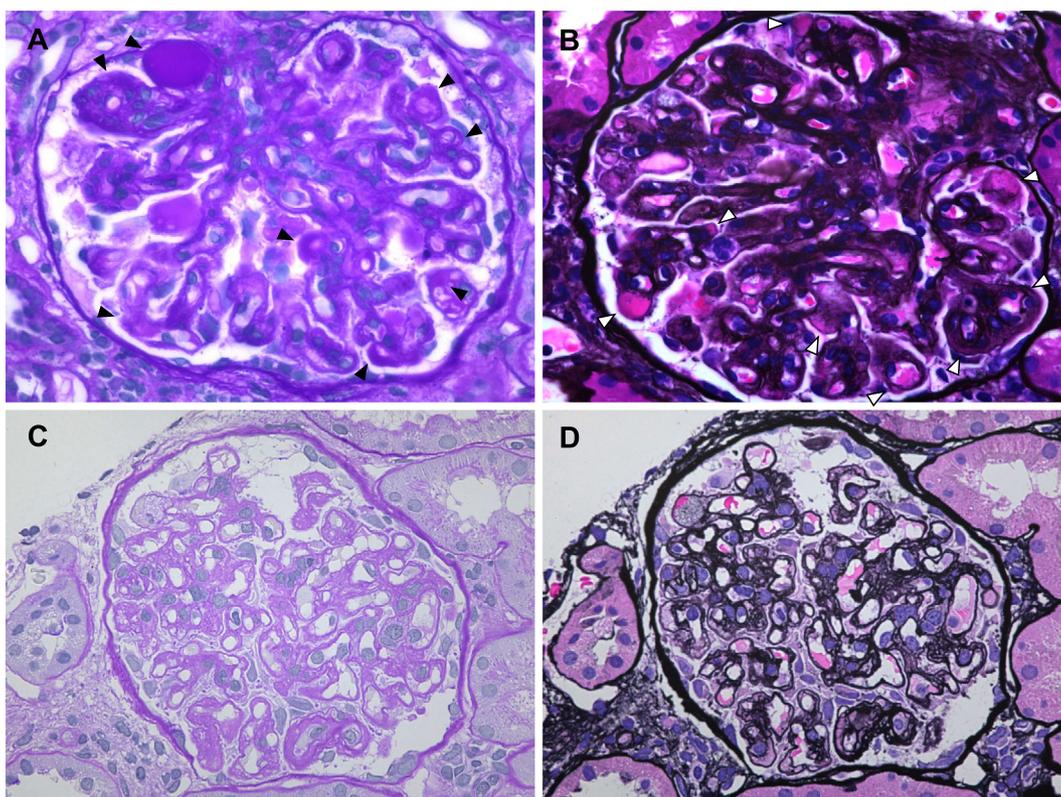


Figure 1. Light microscopic findings. (A, B) Histology of the first kidney biopsy (A) with periodic-acid-Schiff (PAS) staining showed hyaline deposits in the mesangial and subendothelial areas (black arrowheads), and (B) that with periodic-acid-silver methenamine (PASM) staining showed glomerular basement membrane duplication (white arrowheads). (C, D) Histology of the second kidney biopsy (C) with PAS staining showed mesangial and subendothelial hyaline, and (D) that with PASM staining showed extensive duplication of the glomerular basement membrane.

ischemic lesion without cerebral artery stenosis, suggesting the possibility of cerebral embolism. An echocardiogram identified a left ventricular thrombus and dyskinesia of the left ventricular apical segment. According to Mayo Clinic diagnostic criteria (7), the patient was diagnosed with takotsubo cardiomyopathy. Her right arm motor function and left ventricular wall motion completely recovered within a few weeks.

Four months after the diagnosis of takotsubo cardiomyopathy, the serum creatinine level had increased from a baseline of 0.70 to 0.86 mg/dL, and proteinuria was 2.1 g/g Cr. A urinary sediment analysis showed microscopic hematuria with 5 to 9 red blood cells per high-power field. The C3 and C4 levels were within the reference ranges, and testing for hepatitis B virus, hepatitis C virus, and cryoglobulin was negative. M protein was not identified in either serum or urine protein electrophoresis. Serum catecholamine levels were slightly increased, with epinephrine at 100 (reference range, ≤ 100) pg/mL, norepinephrine at 804 (100-450) pg/mL, and dopamine at 21 (≤ 20) pg/mL.

A biopsy of the left kidney was performed. The tissue sample contained 39 glomeruli; 6 glomeruli were globally sclerotic, and 2 were collapsed. The remaining glomeruli contained prominent periodic-acid-Schiff-positive hyaline in the mesangial and subendothelial areas (Fig. 1A). The

glomerular capillary walls were segmentally thickened, and double contour was observed (Fig. 1B). Mild interstitial fibrosis and tubular atrophy involved approximately 10% of the cortex. The arteries showed mild to moderate intimal fibrosis, and the arterioles exhibited hyalinosis. Routine immunofluorescence of frozen tissue showed non-specific positive staining with a segmental pattern along the capillary walls (Fig. 2). Electron microscopy showed subendothelial widening along with a translucent substance (Fig. 3A), possibly suggesting a non-immune-mediated glomerular disease.

Accordingly, the patient was initially diagnosed with membranoproliferative glomerulonephritis (MPGN) without immune deposits, possibly due to glomerular endothelial injury. Her concurrent hypertension and takotsubo cardiomyopathy were considered possible causes of the MPGN pattern of injury.

Four months after the kidney biopsy, the patient's serum creatinine level had increased to 1.03 mg/dL, and her proteinuria had increased to 10.02 g/g Cr, leading to a diagnosis of nephrotic syndrome (Fig. 4). Antihypertensive therapy was started, and subsequently the urinary protein excretion decreased to 0.54 g/g Cr. The patient's home blood pressure was maintained at 120 to 130/70 mmHg after the initiation of renin-angiotensin system inhibition. Two years after the kidney biopsy, the patient's urinary protein had slightly in-

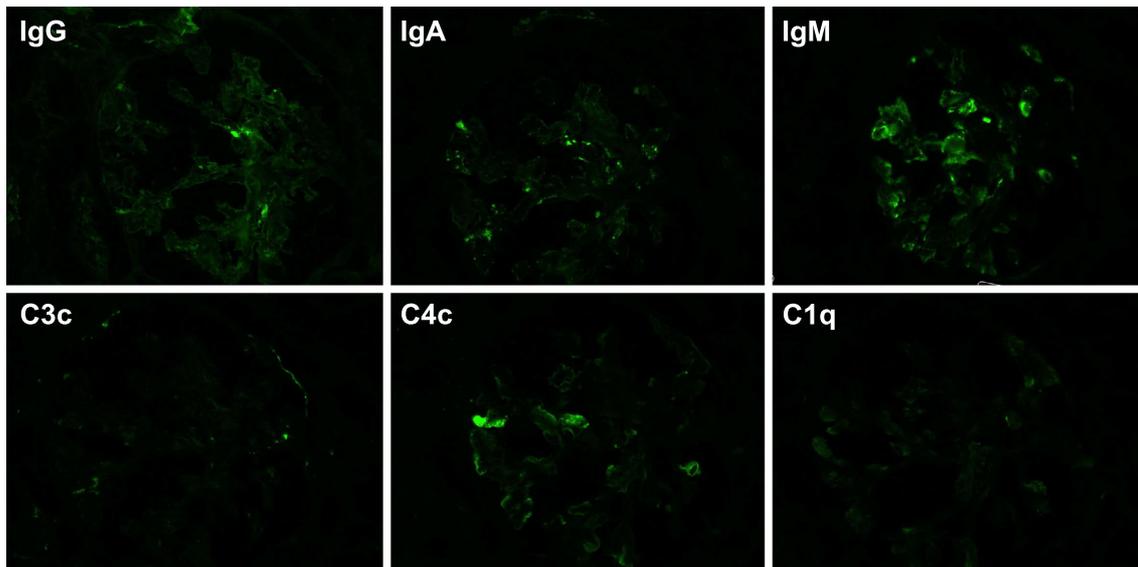


Figure 2. Immunofluorescence images. Routine immunofluorescence of frozen tissue of the first biopsy showed non-specific positive staining with a segmental pattern along the capillary walls.

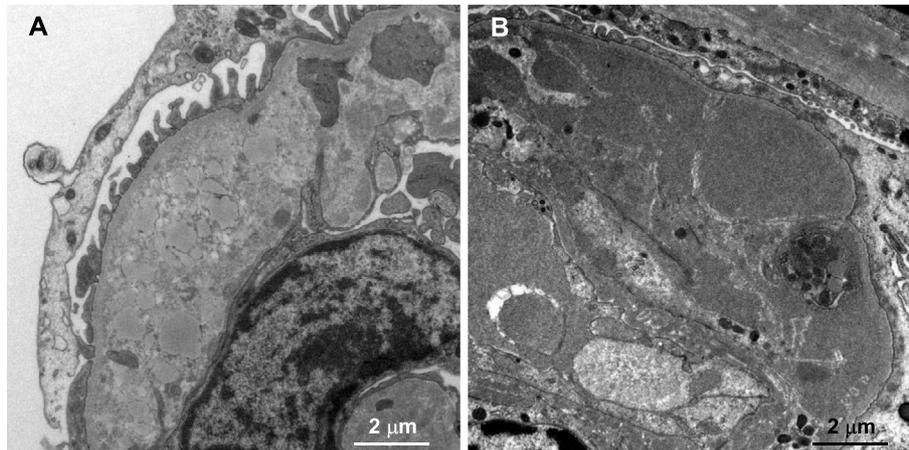


Figure 3. Electron microscopic findings. (A) Electron micrograph of the first biopsy showed a translucent substance over the mesangial and subendothelial areas. (B) Electron micrograph of the second biopsy showed an amorphous electron-dense deposit in the mesangial and paramesangial areas.

creased to 1 to 2 g/g Cr. A second biopsy was then performed.

The tissue sample contained 21 glomeruli; 6 were globally sclerotic, 3 were segmentally sclerotic, and 2 were collapsed. Mesangial hyaline accumulation and duplication of the glomerular basement membrane remained (Fig. 1C, 1D). Interstitial fibrosis and tubular atrophy had progressed and involved 30% of the cortex. A lack of staining with Congo red excluded renal amyloidosis. A routine immunofluorescence assay of the glomeruli was negative. On electron microscopy we found a mesangial and paramesangial substance that had higher electron density than that in the first biopsy (Fig. 3B). These electron microscopic findings suggested the possibility of glomerular disease with non-immune deposits, rather than endothelial injury.

We then carefully reexamined the first biopsy specimen

under scanning electron microscopy and found focally vague fibrillar structures (4-nm diameter) in the translucent substance located in the mesangial area and subendothelial space (Fig. 5A).

Given these results, immunofluorescence staining for fibronectin was performed to evaluate the possibility of fibronectin glomerulopathy. In both the first and second biopsy specimens, the mesangial areas and capillary wall were strongly positive upon staining with IST-4 monoclonal antibody for plasma- and cell-derived fibronectin, whereas staining with IST-9 for cell-derived fibronectin was scant or negative (Fig. 5B, 5C). These immunofluorescence findings allowed a diagnosis of fibronectin glomerulopathy to be made.

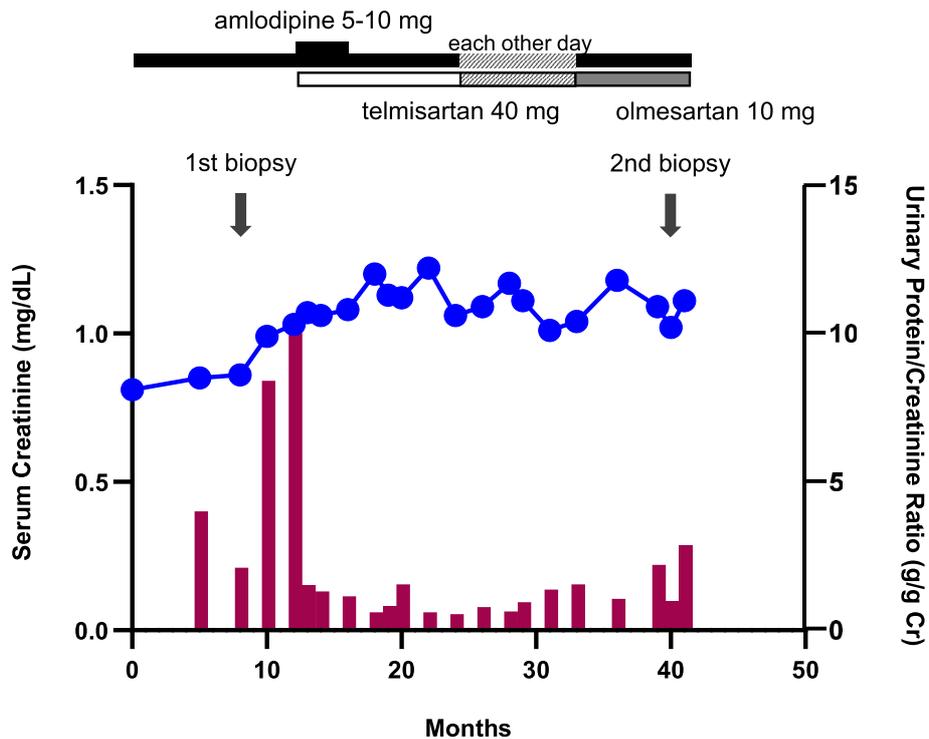


Figure 4. Clinical course. After the diagnosis of takotsubo cardiomyopathy, serum creatinine and urinary protein levels gradually increased. Blood pressure reduction and renin-angiotensin system inhibition partially attenuated the increase in serum creatinine and urinary protein.

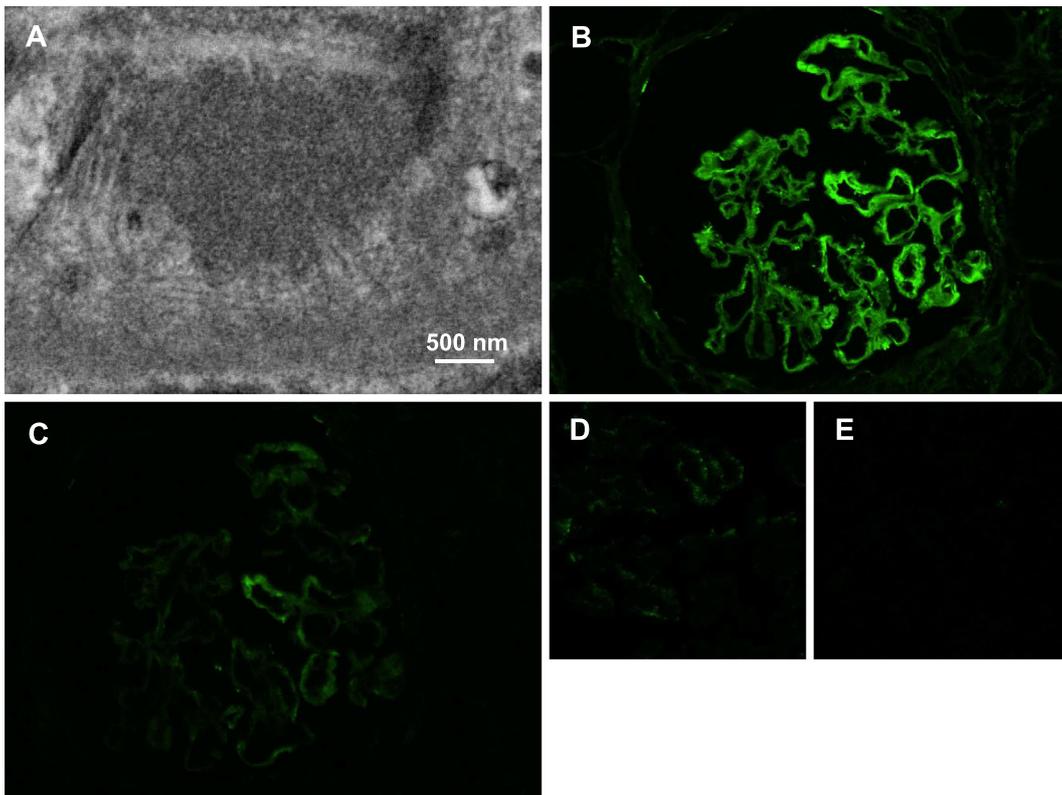


Figure 5. (A) A reexamination of electron micrograph showed focal fibrillary structures in the mesangial area (4-nm diameter fibrils). (B) Immunofluorescence of the second biopsy for plasma- and cell-derived fibronectin (IST-4) showed intense staining in the mesangial areas and capillary wall. (C) Immunofluorescence for cell-derived fibronectin (IST-9) was scant. (D, E) The second biopsy was negative for IgM (D) and C3c (E) immunofluorescence, negating the possibility of exudative lesions.

Discussion

We herein report a case of glomerulopathy that was initially suspected to be an endothelial injury due at least partially to takotsubo cardiomyopathy but was later diagnosed as fibronectin glomerulopathy. Light microscopy at the first biopsy showed an MPGN pattern of injury characterized by mesangial expansion, endothelial swelling, and glomerular basement membrane duplication, resembling features of endothelial injury. The presence of mesangial and subendothelial translucent material on electron microscopy and the lack of specific findings on routine immunofluorescence also suggested the presence of exudative lesions. The patient's background of newly developed hypertension and diagnosis of takotsubo cardiomyopathy might have been factors that led us to misdiagnose endothelial injury at the first biopsy. Both takotsubo cardiomyopathy and fibronectin glomerulopathy are rare diseases, and there are many lessons to be learned from this particular case.

Takotsubo cardiomyopathy is a transient left ventricular dysfunction and accounts for only about 1% of all cases of suspected acute myocardial infarction (4). It causes hemodynamic instability and consequently AKI in approximately 10% to 20% of cases (5, 6). However, no glomerular disease appears to be caused by takotsubo cardiomyopathy. Only one case - of diffuse proliferative exudative glomerulonephritis with crescentic formation - has been reported; the takotsubo cardiomyopathy in that instance was triggered by postinfectious glomerulonephritis, although the causal relationship was not discussed (8).

Endothelial injury is a typical histological finding seen in cases with a non-immune-complex-mediated MPGN pattern. Glomerular endothelial injury can be caused by various diseases, including severe hypertension (9). Catecholamines and inflammatory cytokines are also thought to exacerbate endothelial injury (10, 11). In general, levels of catecholamines are markedly elevated in the acute phase of takotsubo cardiomyopathy (12). In our patient, plasma catecholamine levels were not examined in the acute phase but were slightly elevated four months after the onset of takotsubo cardiomyopathy. Therefore, at the time of the first biopsy, the newly developed hypertension and takotsubo cardiomyopathy were considered potential contributors to the development of an MPGN pattern of glomerular endothelial injury.

A light microscopic examination of the first and second biopsy specimens showed similar MPGN patterns of injury. A comparison of the pathological findings of the first and second biopsies revealed that non-specific IgM and complement trapping was more prominent on immunofluorescence staining from the first biopsy than from the second biopsy (Figs. 2, 5D and 5E) and that the massive amount of substance that had accumulated in the mesangial area of the first biopsy sample was more translucent than that in the second biopsy sample (Fig. 3A, 3B). These differences sug-

gest that endothelial damage may have been present at the first biopsy but had nearly disappeared by the second biopsy. In addition, the transient hemodynamic changes caused by takotsubo cardiomyopathy may have enhanced and irreversibly advanced glomerular lesions against the potentially existing fibronectin nephropathy. Therefore, a reduction in proteinuria through the inhibition of the renin-angiotensin system after the first biopsy may have occurred through attenuation of the takotsubo cardiomyopathy-induced endothelial damage.

The electron-dense material that had accumulated in the mesangial area and subendothelial space was more dense at the second biopsy than at the first, suggesting the possibility of glomerular disease with non-immune deposits rather than endothelial injury. According to the diagnostic algorithm for mesangial extracellular matrix expansion, the presence of extracellular deposits stained negatively with Congo red and negatively for immunoglobulins and complement indicates the possibility of fibronectin glomerulopathy (3, 13). Therefore, we performed immunofluorescence staining for fibronectin and made a final diagnosis of fibronectin nephropathy.

Fibronectin glomerulopathy is a rare, autosomal dominant glomerular disease (1). A quarter of the cases in a literature review had no family history (2). However, patients with sporadic fibronectin glomerulopathy will often never receive a diagnosis due to a lack of rare disease awareness. The presence of comorbidities may lead to a misdiagnosis, as occurred in our patient. The electron-dense deposits of fibronectin glomerulopathy are generally composed of a distinct material that is amorphous or granular and sometimes contain short fibrils measuring 10 to 14 nm in diameter (13). However, these ultrastructural features are not necessary for a definitive diagnosis of fibronectin glomerulopathy and are lacking in most cases. In our patient, the electron microscopic findings at the first biopsy were not a diagnostic clue, as the deposits were loose, and the fibrillar structure was inconspicuous. The endothelial injury due to the hypertension may have modified the glomerular lesions.

In conclusion, this case illustrates the importance of considering fibronectin glomerulopathy in the differential diagnosis of an MPGN pattern of injury with negative findings upon routine immunofluorescence.

This article does not contain any studies with human participants performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

The authors state that they have no Conflict of Interest (COI).

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