The Transition From Minimal Change Disease to Focal and Segmental Glomerulosclerosis in a Patient With Nephrotic Syndrome: a Case Report

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Case Report

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Abstract

Background:

Although minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) have been described as two separate forms of nephrotic syndrome(NS), they are not completely independent. We report a patient presenting a transition from MCD to FSGS, review the literature and explore the relationship between the two diseases.

Case presentation:

A 42-year-old male welder, Asian, presenting lower extremity edema and elevated serum creatinine, had laboratory exams indicating NS and end-stage renal disease(ESRD). The patient had a kidney biopsy 20 years earlier for NS, which indicated MCD, and this repeated kidney biopsy suggested FSGS. After treatment follow-up, the patient was eventually admitted to renal replacement therapy.

Conclusions:

MCD and FSGS may be different stages of the same disease. The transition from MCD to FSGS in this case indicates the progression of the disease, which may be related to the excessive metal caused by occupation.

1. Background

Nephrotic syndrome (NS) is the most common glomerulopathy characterized by nephrotic proteinuria, hypoproteinemia, edema, and hyperlipidemia. Although most patients with NS have similar clinical manifestations, their pathology is quite different. Among them, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the two major forms of NS[1]. In most textbooks, MCD and FSGS are often described as two separate diseases based on their respective characteristics, histology and outcomes. There is still a lot of evidence that they are different manifestations of the same progressive disease [2].

MCD is the most frequent glomerulopathy leading to the NS in childhood, accounting for about 70–90%, while adult MCD accounts for 10–20%[3, 4]. Most MCD patients are responsive to corticosteroids therapy. Acute renal failure occurs in the early stage. Active treatment can achieve complete remission, rarely progression to end-stage renal disease(ESRD). Nephrotic syndrome due to FSGS can appear at any age, taking place in approximately 7–10% of children and 20–30% of adults[5]. Unlike MCD, more FSGS patients are resistant to corticosteroids. Glomerular injury caused by FSGS will lead to irreversible scar formation, which has a poor prognosis and eventually develops to ESRD. Failure to respond to corticosteroids in patients with MCD may predict the presence of FSGS[6].

Although MCD and FSGS are defined as different types of primary glomerular diseases, there is some overlap between them in clinical features and pathological changes. Some scholars have proposed that

they are actually different histological manifestations of the same disease progression, at least some patients have a transition from MCD to FSGS [2, 7].

We report a patient with MCD who entered end-stage renal disease, and the pathological type changed to FSGS after repeated renal biopsy.

2. Case Presentation

A 42-year-old male welder, Asian, presented to our hospital with a chief complaint of bilateral lower extremity edema and elevated serum creatinine for 1 week. Erenow, he had an MCD history dating back 20 years and no other past medical history, including high blood pressure. The patient was diagnosed with NS 20 years ago, and MCD was confirmed by renal biopsy (Fig. 1, Fig. 2).

At that time, the patients were regularly treated with corticosteroids. First prescribed prednisolone 40mg/day, and then gradually tapered and stopped within 12 months. After treatment, the clinical symptoms of NS were completely relieved, and the urine test turned negative. His NS did not relapse in the following period after discontinuation of the corticosteroids, but the patient was not regularly reviewed, urine tests and renal function were unknown.

On admission, the vital signs of the patient were stable, and no evident abnormality was found in the physical examination except mild edema in both his lower extremities. The results of his laboratory tests showed urinalysis: protein 3+, occult blood 3+, red blood cells(RBC)18–20/HP, Glucose 3+, ketones -; 24-hour urinary protein quantitation 10920.0mg/24h; serum albumin: 22.3 g/L; serum creatinine: 1096 μmmol/L; urea: 34.26μmmol/L; CKD-EPI estimated GFR ¼ 4.4 mL/min/1.73 m2; blood cadmium (Cd) 2.8μg/L and blood lead (Pb) 32.8μg/L; Urine metal elements, plasma complement C3, C4, serum and urine free light chain, immunofixation electrophoresis, anti-GBM antibody, ANCA, antinuclear antibody series, serology for HBV, HCV, HIV and PLA2R were negative. His nephrosonography revealed enhanced echogenic parenchyma without significant renal shrinkage. Echocardiography, renal artery ultrasound and chest CT were normal. Therefore, he was initially diagnosed with NS, ESRD.

Our first diagnosis was MCD - induced acute kidney injury (AKI). Considering that the patient had reached ESRD level, the reexamination showed no recovery trend of serum creatinine, and urgent hemodialysis treatment was performed. During dialysis, he began to take prednisolone acetate tablets orally at a dose of 30mg/d, and other adjuvant therapies included diuretics and Traditional Chinese Medicine. However, after 1 month of treatment, the edema of the patient was relieved, and the renal function did not improve significantly. The previous renal biopsy of the patient indicated MCD, which prognosis is good and was insufficient to explain the current ESRD. After obtaining the consent of the patient, we performed a repeat renal biopsy and the results indicated FSGS (Fig. 3, Fig. 4).

Coupled with the renal biopsy results, the patient entered renal replacement therapy with rapid corticosteroids reduction and withdrawal. During the follow-up period of 1 year, the patient was negative

for metal elements in blood and urine after resignation. His renal function partially recovered, but no signs of dialysis detachment were discovered.

3. Discussion

Our patient underwent a renal biopsy at the time of initial diagnosis of NS, which pathologically revealed MCD. MCD is considered to be a benign disease with a favorable long-term prognosis and a rare tendency to progress to ESRD. There was no glomerular injury under light microscopy, and only the foot process of podocytes disappeared under electron microscopy, but not the loss of the podocytes themselves[8]. Although the proportion of adult-onset MCD patients in NS is low, unlike children, it is less responsive to corticosteroids and more prone to AKI. Moreover, steroid-resistant MCD patients may progress to ESRD, and these patients may be missed FSGS patients. In contrast to MCD, patients with FSGS have a higher risk of corticosteroid-resistant and renal failure. Irreversible glomerular damage caused in the context of FSGS can be explained by podocyte depletion. Compensatory hypertrophy of the remaining podocytes, cell-to-cell propagation of podocyte injury, and segmental solidification of the glomerular tuft can lead to progressive focal and segmental sclerosis[5, 9].

As far as we know, cases of transition between MCD and FSGS are not rare in clinical practice, but few cases have been reported. Only some cases have appeared in observational studies without in-depth analysis, and most of these studies were concentrated in children or adolescence [10, 11, 12]. In the above literature, most scholars may prefer to have FSGS at the beginning of the disease. The focal and segmental nature of FSGS leads to sample error or diagnosis error, resulting in misdiagnosis of MCD or missed diagnosis of FSGS. We agree that, especially in patients with early lesions or few glomeruli in biopsy specimens. Early FSGS could only show the diffuse effacement of the foot process, which was consistent with MCD. There was no difference in the decrease of podocyte density labeled by WT1 between MCD and FSGS[13]. These factors can result in confusion of the two diseases for clinicians. In fact, FSGS lesions may be absent in the early stages of NS, and the presence of FSGS lesions in repeated biopsy tissue reflects the progression of MCD. The dose dependence of animal models supports the hypothesis that MCD and FSGS are two successive pathological processes of podocyte disease. Both models are based on the induction of podocyte injury and subsequent podocyte loss, and the difference depends on the degree of podocyte injury and severity of podocyte loss. Only foot process of podocyte exfoliation similar to MCD is observed at the initial phase, while persistent podocyte loss results in the development of FSGS[14]. In the initial stages, this disease is steroid-sensitive. With relapse and delay, continuous proteinuria and podocyte loss lead to decreased or lost of steroid sensitivity. When the loss of podocytes is more than 30–40%, the outcome of ESRD seems inevitable [2]. In this case, after the diagnosis of MCD, the patient was treated regularly with corticosteroid and achieved complete remission. Although there was no regular follow-up later, at least it was not a serious relapse, according to his description. It has been 20 years since the typical NS recurrence, and his clinical course and repeated renal biopsy results both support FSGS. In order to avoid misdiagnosis, we found the kidney tissue from 20 years ago for re-pathological examination, and the results still support MCD. Therefore, we infer that the patient progressed from MCD to FSGS, rather than a missed diagnosis of FSGS at the first diagnosis.

It is no coincidence that pathological changes occurred before and after repeated renal biopsy. Primary FSGS is usually caused by circulating factors, and the aetiology of secondary FSGS includes infection, drugs, maladaptive responses, familial /genetic form, variation of APOL1 gene and so on[15, 9]. The patient did not have the above background, but a suspiciously related factor was his occupation. He was an electric welder with excessive levels of cadmium and lead in his blood. We have reason to suspect that his aggravation of pathology or the occurrence of ESRD was related to metal nephrotoxicity. The nephrotoxicity induced by excess exposure to certain metals is well known, and lithium has been shown to cause FSGS[16]. Cadmium and lead exposure to the kidney mainly causes proximal renal tubule dysfunction, acute exposure can lead to Fanconi syndrome, and long-term exposure leads to the persistent decline of renal function[17, 18]. Although there is not enough literature to confirm that lead and cadmium can cause FSGS, it has been proved that both of them have podocytotoxicity and even induce podocyte apoptosis [19, 20]. Lead and cadmium can increase the risk of chronic kidney disease respectively, and the combination of the two has more profound nephrotoxicity [21]. The above may explain the positive urine sugar of the patient, and presumably, it may be the reason for the occurrence of ESRD in this patient.

Unfortunately, the patient ultimately required renal replacement therapy, but this case was thought-provoking. MCD and FSGS are both representative podocyte diseases, clinically presenting as sudden-onset NS, characterized by absence of immune deposits in immunofluorescence[22]. However, their treatment responses and the prognosis are quite different. The differential diagnosis of MCD and FSGS is difficult, but it is very important to distinguish between the two. A positive attitude toward a second or multiple renal biopsies is needed for uncertain or recurrent MCD patients and early FSGS patients. In addition to the invasive operation of renal puncture, urinary myo-inositol, PEC marker staining and IgG/albumin staining ratio in tPRD are also potential diagnostic markers to differentiate MCD and FSGS[23, 24, 25].

4. Conclusion

Through this case and literature study, we realized that FSGS could be the late stage of MCD, and FSGS lesions found in repeated renal biopsy can often reflect the progression of the disease. Patients with MCD who have a slower and less effective response to hormones should be alert to the risk of conversion to FSGS, as well as the possibility of co-existing FSGS lesions. Due to its focal and segmental nature, it puts forward higher requirements for renal biopsy surgeons, at least to ensure the number of glomeruli.

Abbreviations

MCD: minimal change disease

FSGS: focal segmental glomerulosclerosis

NS: nephrotic syndrome

ESRD: end-stage renal disease

AKI: acute kidney injury

ANCA: anti-neutrophil cytoplasmic antibodies

PLA2R: phospholipase A2 receptor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

We obtained the patient's informed consent to publish this case and accompanying data and images.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Long Tang obtained and interpreted the patient clinical data, wrote and finally submitted the manuscript. Long Tang and Zhen Cai performed the histological examination of the kidney, and were major contributors in writing the manuscript. Yuan Meng participated in analysis of patient pathological data. Wen-jing Zhao and Su-Xia Wang critically reviewed and revised the final manuscript, and were consultants during the treatment and getting to the final diagnosis. All authors read and approved the final manuscript.

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Footnotes

Long Tang is the first author. Long Tang and Zhen Cai contributed equally to this work.

References

1. Candelier JJ, Lorenzo HK. Idiopathic nephrotic syndrome and serum permeability factors: a molecular jigsaw puzzle. Cell Tissue Res. 2020 Feb;379(2):231-243.
2. Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Minimal change disease and idiopathic FSGS: manifestations of the same disease. Nat Rev Nephrol. 2016 Dec;12(12):768-776.
3. Meyrier A, Niaudet P. Acute kidney injury complicating nephrotic syndrome of minimal change disease. Kidney Int. 2018 Nov;94(5):861-869.
4. Sasaki T, Tsuboi N, Marumoto H, Okabayashi Y, Haruhara K, et al. Nephron Number and Time to Remission in Steroid-Sensitive Minimal Change Disease. Kidney Med. 2020 Aug 1;2(5):559-568.
5. Shabaka A, Tato Ribera A, Fernández-Juárez G. Focal Segmental Glomerulosclerosis: State-of-the-Art and Clinical Perspective. Nephron. 2020;144(9):413-427.
6. Wang CS, Greenbaum LA. Nephrotic Syndrome. Pediatr Clin North Am. 2019 Feb;66(1):73-85.
7. Müller-Deile J, Schenk H, Schiffer M. Minimal-change-Glomerulonephritis und fokal-segmentale Glomerulosklerose [Minimal change disease and focal segmental glomerulosclerosis]. Internist (Berl). 2019 May;60(5):450-457.
8. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal Change Disease. Clin J Am Soc Nephrol. 2017 Feb 7;12(2):332-345.
9. Rosenberg AZ, Kopp JB. Focal Segmental Glomerulosclerosis. Clin J Am Soc Nephrol. 2017 Mar 7;12(3):502-517.
10. Ahmad H, Tejani A. Predictive value of repeat renal biopsies in children with nephrotic syndrome. Nephron. 2000 Apr;84(4):342-6.
11. Maas RJ, Deegens JK, Beukhof JR, Reichert LJ, Ten Dam MA, et al. The Clinical Course of Minimal Change Nephrotic Syndrome With Onset in Adulthood or Late Adolescence: A Case Series. Am J Kidney Dis. 2017 May;69(5):637-646.
12. Wieder N, Greka A. Calcium, TRPC channels, and regulation of the actin cytoskeleton in podocytes: towards a future of targeted therapies. Pediatr Nephrol. 2016 Jul;31(7):1047-54.
13. da Silva CA, Monteiro MLGDR, Araújo LS, Urzedo MG, Rocha LB, et al. In situ evaluation of podocytes in patients with focal segmental glomerulosclerosis and minimal change disease. PLoS One. 2020 Nov 4;15(11):e0241745.
14. Pippin JW, Brinkkoetter PT, Cormack-Aboud FC,et al. Inducible rodent models of acquired podocyte diseases[J]. Am. J. Physiol. Renal Physiol. 2009,296(2):213–229.
15. Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. Nat Rev Nephrol. 2015 Feb;11(2):76-87. doi: 10.1038/nrneph.2014.216. Epub 2014 Dec 2. PMID: 25447132; PMCID: PMC4772430.

16. Gong R, Wang P, Dworkin L. What we need to know about the effect of lithium on the kidney. Am J Physiol Renal Physiol. 2016 Dec 1;311(6):F1168-F1171.
17. Orr SE, Bridges CC. Chronic Kidney Disease and Exposure to Nephrotoxic Metals. Int J Mol Sci. 2017 May 12;18(5):1039.
18. Satarug S, Gobe GC, Ujjin P, Vesey DA. A Comparison of the Nephrotoxicity of Low Doses of Cadmium and Lead. Toxics. 2020 Mar 2;8(1):18.
19. Eichler TE, Ransom RF, Smoyer WE. Differential induction of podocyte heat shock proteins by prolonged single and combination toxic metal exposure. Toxicol Sci. 2005 Mar;84(1):120-8.
20. Eichler T, Ma Q, Kelly C, Mishra J, Parikh S, et al. Single and combination toxic metal exposures induce apoptosis in cultured murine podocytes exclusively via the extrinsic caspase 8 pathway. Toxicol Sci. 2006 Apr;90(2):392-9.
21. Andjelkovic M, Buha Djordjevic A, Antonijevic E, Antonijevic B, Stanic M, et al. Toxic Effect of Acute Cadmium and Lead Exposure in Rat Blood, Liver, and Kidney. Int J Environ Res Public Health. 2019 Jan 18;16(2):274.
22. Ahn W, Bomback AS. Approach to Diagnosis and Management of Primary Glomerular Diseases Due to Podocytopathies in Adults: Core Curriculum 2020. Am J Kidney Dis. 2020 Jun;75(6):955-964.
23. An JN, Hyeon JS, Jung Y, Choi YW, Kim JH, et al. Urinary myo-inositol is associated with the clinical outcome in focal segmental glomerulosclerosis. Sci Rep. 2019 Oct 11;9(1):14707.
24. Suzuki T, Kohatsu K, Han W, Watanabe S, Yahagi K, et al. Morphological Features of Minimal Change Disease and Focal Segmental Glomerulosclerosis Using Repeat Biopsy and Parietal Epithelial Cell Marker. Kidney Dis (Basel). 2020 Mar;6(2):119-124.
25. Bu L, Mirocha J, Haas M. Immunoglobulin G/albumin staining in tubular protein reabsorption droplets in minimal change disease and focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2020 Mar 19:gfaa039. doi: 10.1093/ndt/gfaa039.

Figures

Fig. 1

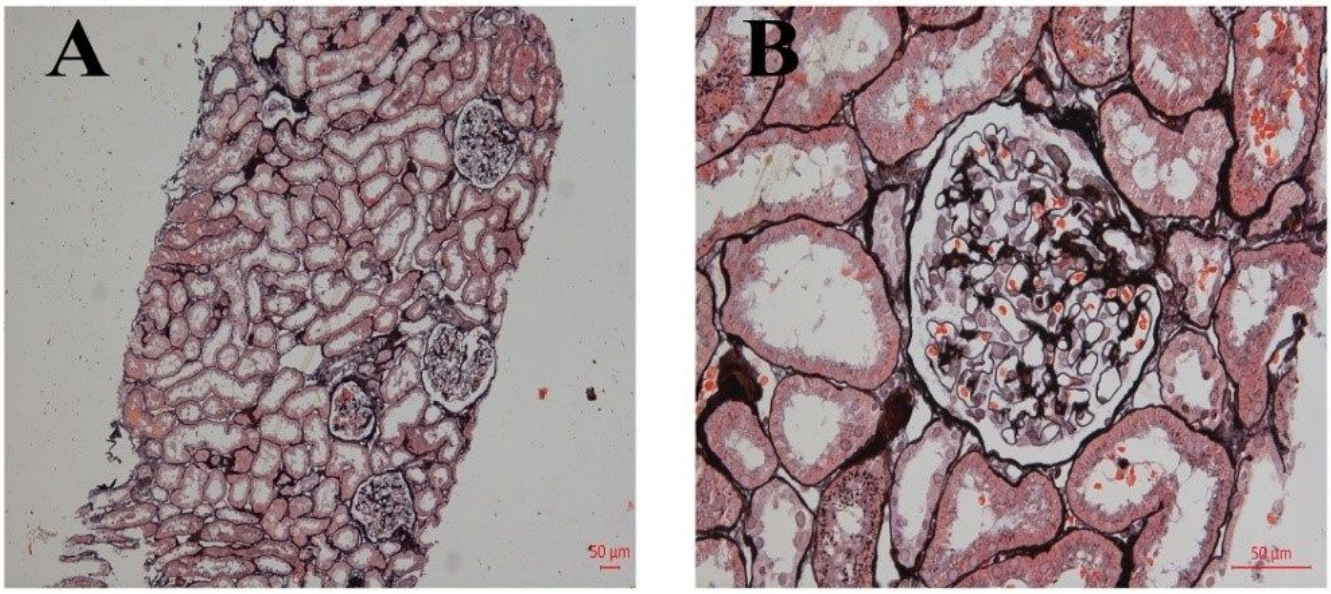

Figure 1

Light microscopy of histological changes of renal biopsy 20 years ago. Vacuolar degeneration of glomerular capillary basement membrane, renal tubular epithelial cells vacuoles and granular degeneration , no obvious lesions in renal interstitium and arterioles (PASM, Ax 100; Bx400).

Fig. 2

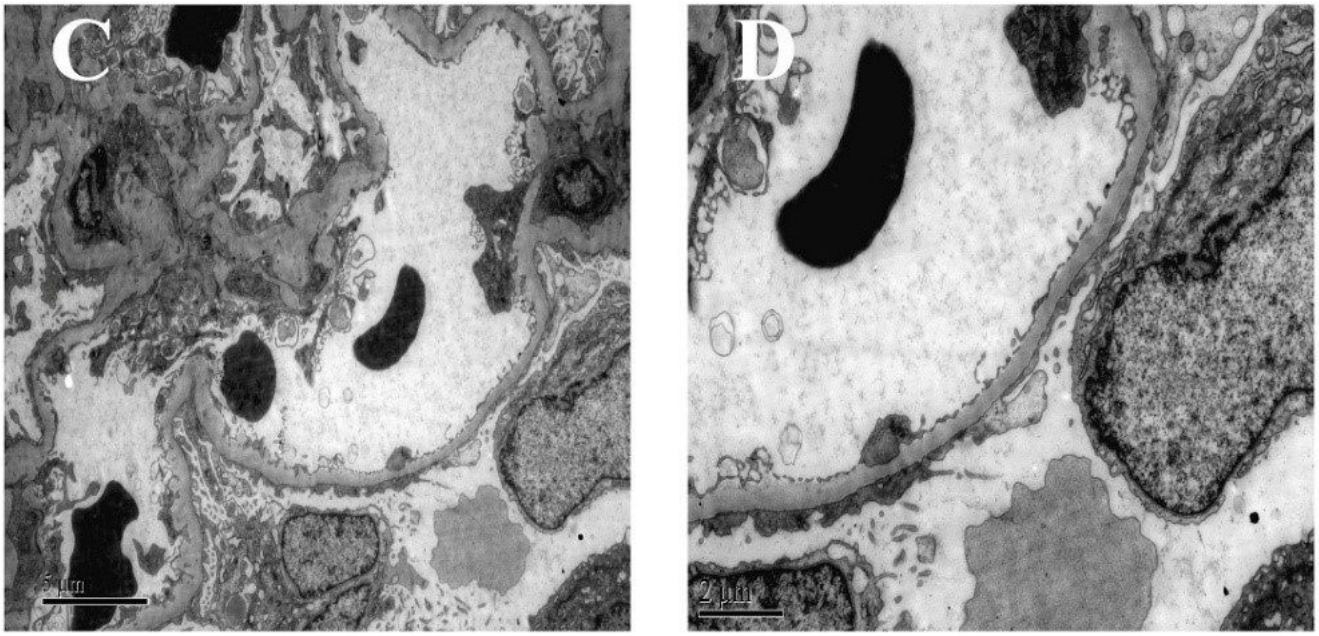

Figure 2

Electron microscopy of histological changes of renal biopsy 20 years ago. Extensive fusion of foot process of glomerular visceral epithelial cells (Cx6000; Dx12000).

Fig. 3

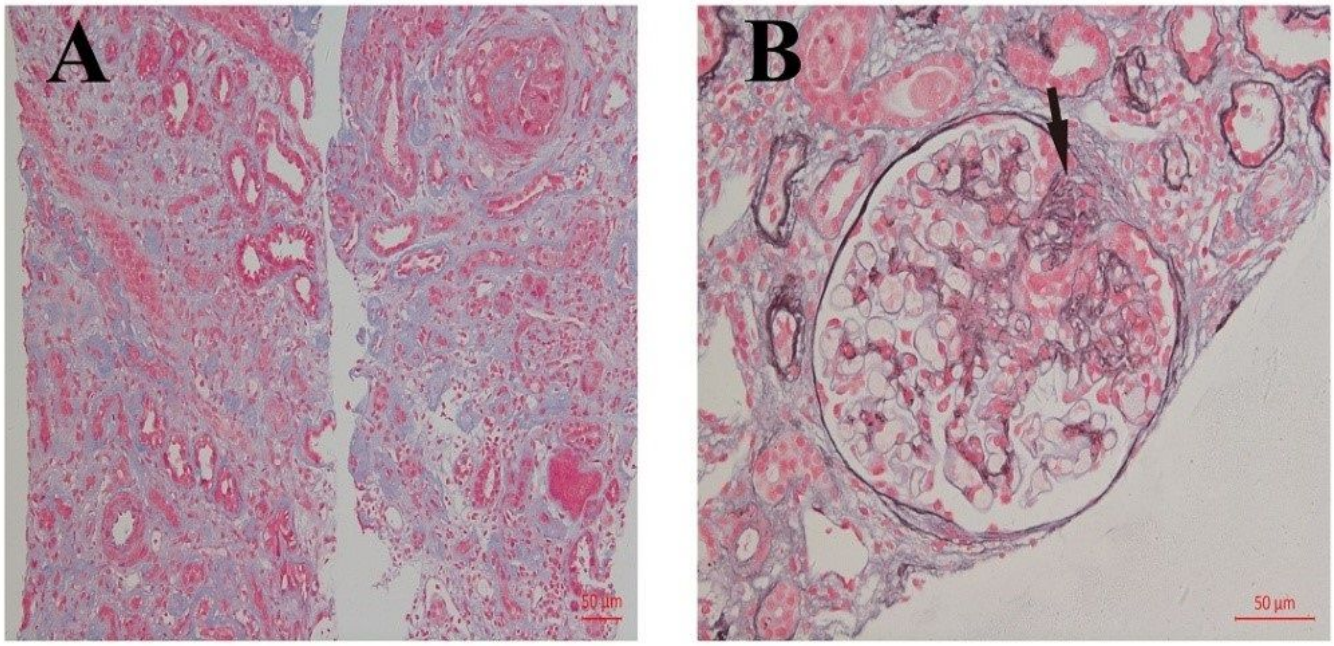

Figure 3

Light microscopy of histological changes of renal biopsy after 20 years. Multifocal and patchy atrophy of renal tubules, multifocal and patchy lymphocytic infiltration of renal interstitium with fibrosis, and thickening of arterioles (Masson, Ax200). Mild segmental hyperplasia of glomerular mesangial cells and matrix, and segmental sclerosis (↑) can be seen (PASM, Bx400).

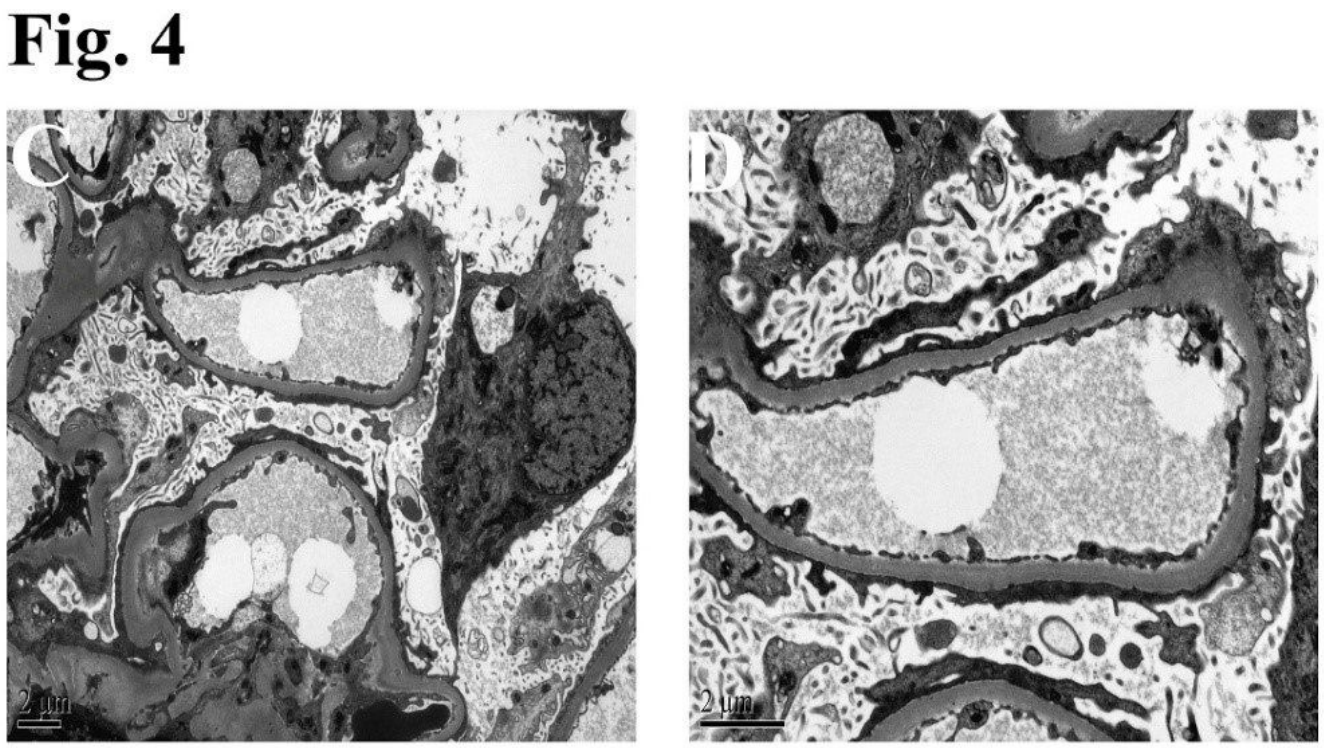

Figure 4

Electron microscopy of histological changes of renal biopsy after 20 years. Microvillous transformation of podocytes and extensive fusion of foot processes (Cx6000; Dx12000).

Supplementary Files

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