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Chronic Diseases and Translational Medicine

CORRESPONDENCE

IgA nephropathy with podocytic infolding glomerulopathy

Dear Editor,

Podocytic infolding glomerulopathy (PIG) is a glomerular disease characterized by specific structures of the thickened glomerular basement membrane (GBM), including microspheres, microtubular structures, and podocytic infolding. It was first reported in 1992 by Sato et al.[1] This type of glomerulopathy has not been included in the World Health Organization's classification of glomerular diseases. The concept of PIG was then proposed in 2008 by the Japanese Society of Nephrology according to electron microscopic findings from renal biopsies of 25 patients in Japan. The diagnostic criteria included nonargyrophilic holes in the GBM by light microscopy and microspheres and/or microtubules of 50–150 nm within the GBM by electron microscopy. PIG is divided into three types: type A with only primary podocytic infolding, Type B with both primary podocytic infolding and microstructures in the GBM, and type C with only microstructures in the GBM.[2] Some studies on pathogenic mechanisms suggest a potential association with complement activation.[3–5] To date, 45 cases of PIG have been reported worldwide.[6,7] The reported patients exhibited proteinuria, hematuria, hypertension, and normal or abnormal renal function. Some of them were diagnosed with connective tissue diseases (CTD) such as systemic lupus erythematosus (SLE) and Sjögren syndrome. Here, we present a case of PIG with immunoglobulin A nephropathy (IgAN). This case expands the disease spectrum of PIG and increases the total number of PIG cases to 46.

A 60-year-old woman was admitted to our hospital in December 2019, complaining of proteinuria for 9 years and pitting edema in both lower extremities for 5 days. Nine years ago, she developed proteinuria. Laboratory examination revealed that urinary protein was 0.18 g/day and that serum creatinine was normal. Hence, a renal biopsy was not performed. Urinalysis revealed 116 leukocytes/μL, hematuria (+++). She was diagnosed with glomerulonephritis and treated with glucocorticoid (the specific dose is unknown) for 3 months. Then, she was treated with leflunomide and allisartan isoproxil. The level of proteinuria fluctuated by 1 g/24 h. Hydroxychloroquine was given since April 2019. In December 2019, she was admitted to our hospital with pitting edema in her lower extremities. The urine routine showed protein ++ and red blood cell +−. The urinary albumin-to-creatinine ratio was 2.11 g/mol. The level of blood albumin was 35.8 g/L, and the level of serum creatinine was 39.0 μmol/L. She had no hepatitis, human immunodeficiency virus, and syphilis infection. The markers of autoimmune diseases, ANA, PR3-ANCA, and MPO-ANCA, were negative. The anti-GBM antibody and anti-PLA2R antibody were not detected. She had a history of osteoarthritis. A renal biopsy was performed. Immunofluorescence revealed four glomeruli with moderate granular deposits of IgA on the mesangial areas, and negative for IgG, IgM, C3, and Fibrin (Figure 1A). Light Microscopy showed 21 glomeruli with mild thickening capillary walls, the segmental proliferation of mesangial area (3–4 cells/proliferation area), mild segmental expansion of mesangial matrix, and podocyte swelling without endothelial cell proliferation. There was no crescent formation or adhesion. No obvious deposition of erythrophilic protein was detected by Masson staining. The renal interstitium had mild swelling and fibrosis, infiltrated by discrete lymphocytes and plasma cells. Arteriole walls in the renal interstitium were not thickened. The renal pathology was consistent with IgAN (Oxford classification: M0 E0 S0 T0 C0) shown in Figure 1B. Electron microscopy showed mild, segmental proliferation of mesangial cells and mesangial matrix. GBM had segmental thickening, stratification with podocytic infolding and microspheres, and subepithelial scattered granular electron-dense deposits with extensive foot process effacement (Figure 1C). PLA2R and IgG4 staining were negative (Figure 1D,E). This case was diagnosed with IgAN with PIG.

This middle-aged female patient was admitted due to proteinuria, hematuria, and edema with normal renal function without secondary causes. This was the first reported case of IgAN diagnosed with PIG and the 46th case of PIG. Of the 46 reported PIG patients, 27 patients (58.7%) are in Japan, 16

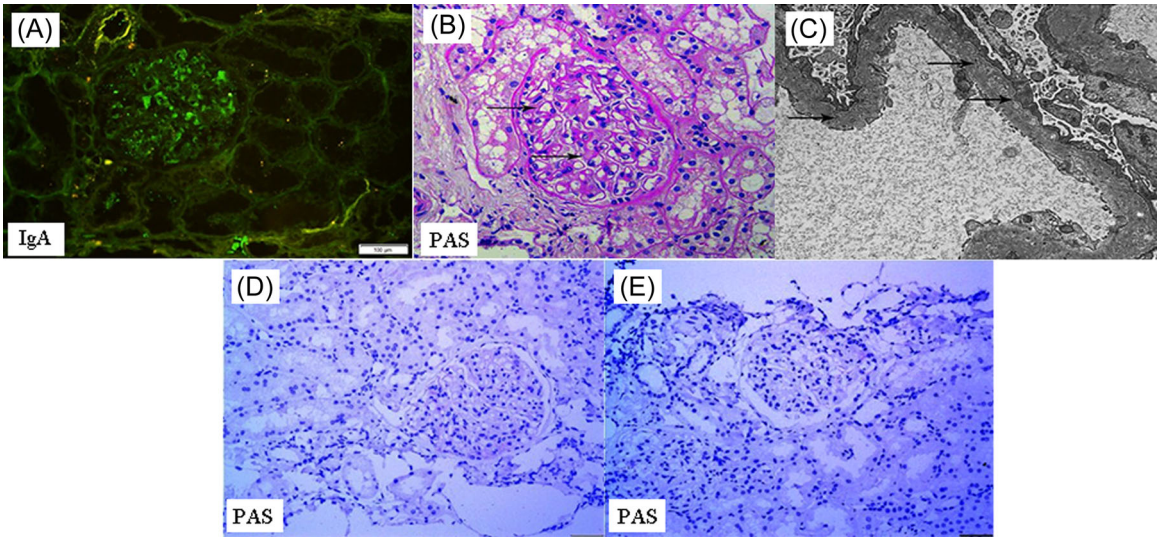

FIGURE 1 Renal biopsy findings (A–E). (A) Immunofluorescence staining showed moderate IgA depositions in the mesangial areas (++) of glomeruli (Bars = 100 μm). (B) Segmentally mild mesangial proliferation and mesangial matrix expansion (arrowhead) with mild thickening of glomerular capillary walls (PAS, ×400). (C) Electronic microscopy showed segmental thickening of the glomerular capillary wall basement membrane, there are microspheres and plasma membrane-like and vacuole-like structures in the basement membrane (arrowheads) (×15,000). Immunohistochemistry staining of glomeruli showed that PLA2R (D) and IgG4 (E) staining were negative. (PAS, ×100). IgA, immunoglobulin A.

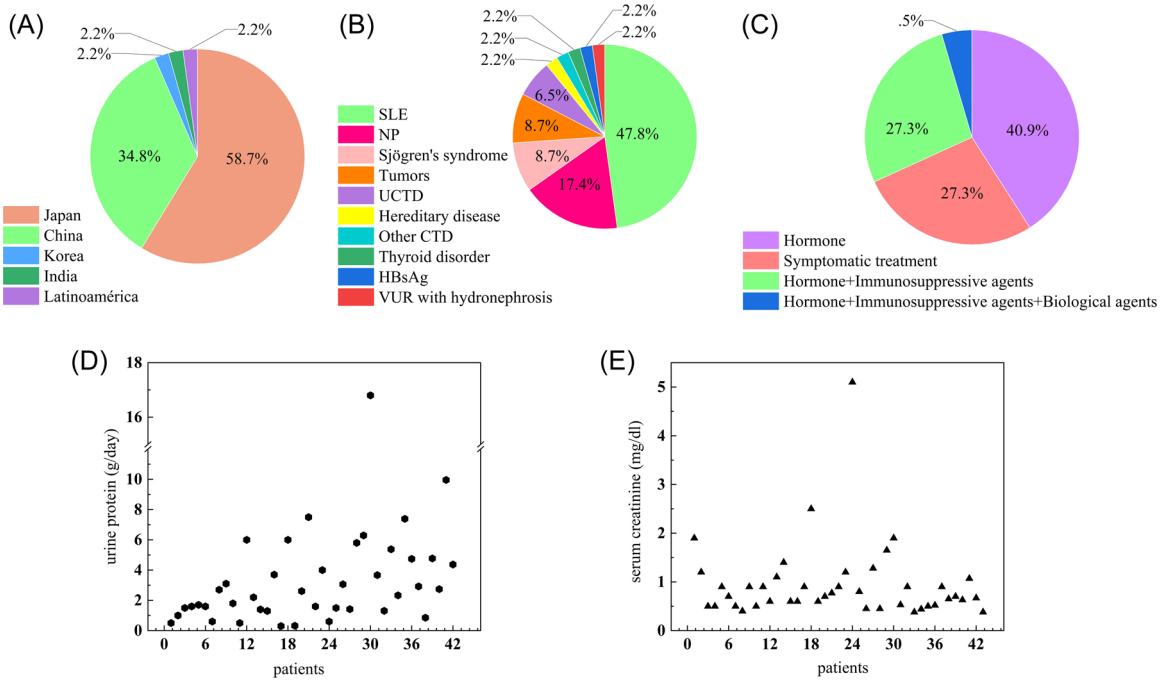

FIGURE 2 Clinical characteristics of the PIG patients (A–E). (A) National distribution of PIG is 58.7% from Japan and 34.8% from China. (B) Concomitant disease of PIG, SLE was the most common disease. (C) Treatment for PIG patients. (D) The level of urine protein of PIG patients. (E) The serum creatinine level of PIG patients. CTD, connective tissue diseases; PIG, podocytic infolding glomerulopathy; SLE, systemic lupus erythematosus.

patients (34.8%) are in China, and the remaining three patients (2.2%) are from Korea, India, and Latino America, respectively. 45 cases have been reported in Asia, accounting for 97.8% of the global cases (Figure 2A).

The pathogenic mechanism of PIG has not been clarified. Nakajima et al.[3] demonstrated that C1s, C3d, and C9 were positive in some microstructures, suggesting that activation of the complement pathway may play an important role in the formation of

microstructures. Higlais et al.[4] found that C5b-9 membrane attack complex was positive by immunohistochemical detection, and speculated that the podocyte invagination may be related to the in situ activation of the complement. Fujigaki et al. revealed that some intra-GBM microstructures were connected with podocytes.[5] The podocyte and GBM injuries caused by C5b-9 might in part contribute to podocytic infolding and intra-GBM microstructures.

Light microscopic features of the 46 reported cases included lupus nephritis (LN), membranous nephropathy, focal segmental glomerulosclerosis, and minor glomerular abnormality. LN was the most common pathological manifestation. Electron-dense deposits in the GBM were found in 8 (17.4%) of 46 patients. The thickened GBM was reported in 44 (95.7%) cases. Fourteen (30.4%) cases were negative in immunofluorescent staining. Nineteen (41.3%) cases presented immunoglobulin deposition and 14 (30.4%) patients with both immunoglobulin and complement deposition. The renal pathology of our patient was only IgA deposition in the mesangium.

There were 36 women and 10 men. The ages ranged from 20 to 79 years old. The clinical manifestations were nephrotic syndrome or asymptomatic proteinuria, microscopic hematuria, and hypertension. Proteinuria was the main clinical manifestation (Figure 2D). The level of proteinuria ranged from 0.3 g/24 h to 16.8 g/24 h. A percentage of 34.8% of patients showed massive proteinuria (>3.5 g/24 h). Fourteen (30.4%) patients had proteinuria less than 1.5 g/24 h. The majority of the patients had normal renal function while the minority progressed to renal dysfunction[8] (Figure 2E). Thirty (65.2%) patients were diagnosed with CTD (Figure 2B), of which 22 (73.3%) were SLE. There were two patients accompanied with nonimmune glomerular disease (multiple myeloma, diffuse large B cell lymphoma). This patient was a 60-year-old female with no secondary causes. The diagnosis of IgAN with PIG was confirmed based on clinical and pathological profiles. The clinical manifestations were consistent with previously reported cases. But, IgAN with PIG was not reported in the previous literature. This case expands the disease spectrum of PIG. Also, it provides evidence that PIG is a disease independent of CTD.

There is no consensus on the treatment of PIG. It was reported that urine protein reduced, even turned negative after glucocorticoid alone or with immunosuppressive agent treatment in most patients.[2,9,10] Except for one patient who was not reported in detail, 18 (39.1%) patients were treated with glucocorticoid therapy alone. Fifteen (32.6%) patients received glucocorticoid and immunosuppressive agents including mycophenolate mofetil, cyclosporine, hydroxychloroquine, and tacrolimus. Glucocorticoids, immunosuppressive agents, and biological agents were administered to two (4.3%) patients (Figure 2C) including rituximab and belimumab. The level of proteinuria decreased with administration in 35 (71.7%) patients. Six (13.0%) patients had recurrence or deterioration.[11] The proteinuria level of this case decreased after treatment with leflunomide and hydroxychloroquine.

In conclusion, the clinical characteristics of this patient were consistent with the previously reported cases. But, the pathological diagnosis of this case was IgAN with PIG. This case expands the disease spectrum of PIG. PIG is mainly reported in cases at present. There are few reports about the specific pathogenesis and treatment of PIG. It deserves more attention and further investigation to promote awareness of PIG.

AUTHOR CONTRIBUTIONS

Zhouyang Wang reviewed the literature and wrote the manuscript. Yujie Diao, Zhendong Wang, and Xiangdong Yang reviewed the literature and made revisions, Junhui Zhen and Guangyi Liu supervised and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Qilu Hospital of Shandong University. Written informed consent to participate in this study was provided by the participants' legal guardian next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

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REFERENCES

1. Sato H, Saito T, Yoshinaga K. Intramembranous fine deposit disease associated with collagen disorders: a new morphological entity? *Virchows Arch A Pathol Anat Histopathol*. 1992;420(5):447-451. doi:10.1007/BF01600517
2. Joh K, Taguchi T, Shigematsu H, et al. Proposal of podocytic infolding glomerulopathy as a new disease entity: a review of 25 cases from nationwide research in Japan. *Clin Exp Nephrol*. 2008;12(6):421-431. doi:10.1007/s10157-008-0104-z
3. Nakajima M, Hewitson TD, Mathews DC, Kincaid-Smith P. Localisation of complement components in association with glomerular extracellular particles in various renal diseases. *Virchows Arch A Pathol Anat Histopathol*. 1991;419:267-272.
4. Hinglais N, Kazatchkine MD, Bhakdi S, et al. Immunohistochemical study of the C5b-9 complex of complement in human kidneys. *Kidney Int*. 1986;30(3):399-410. doi:10.1038/ki.1986.198
5. Fujigaki Y, Muranaka Y, Sakakima M, et al. Analysis of intra-GBM microstructures in a SLE case with glomerulopathy associated with podocytic infolding. *Clin Exp Nephrol*. 2008;12(6):432-439. doi:10.1007/s10157-008-0095-9
6. Feng Y, Wang W, Zou Y, et al. Podocyte infolding glomerulopathy: a case series report and literature review. *J Clin Med*. 2023;12(3):1088. doi:10.3390/jcm12031088
7. Kim C, Tan RYP, Tan J, et al. Patterns of podocyte infolding glomerulopathy and collapsing glomerulopathy seen in a patient with systemic lupus erythematosus: a case study. *Pathology*. 2023;s0031-3025(23):00093-4. doi:10.1016/j.pathol.2023.02.005
8. Zhang T, Sun W, Xue J, et al. Podocytic infolding glomerulopathy: two new cases with connective tissue disease and literature review. *Clin Rheumatol*. 2019;38(5):1521-1528. doi:10.1007/s10067-019-04504-6
9. Xu F, Zhu X, Zeng C, et al. Podocyte invagination glomerular disease. *Chin J of Nephrol, Dial. Transplant*. 2015;24(4):391-394.
10. Xu D, Zhu S, Geng J, et al. Systemic lupus erythematosus complicated with podocyte invagination glomerular disease: a case report. *Trauma and Crit Care Med*. 2018;6(03):191-192.
11. Xu D, Zhu S, Geng J. A case of systemic lupus erythematosus complicated with podocyte invaginated glomerulopathy. *Trauma and Crit Care Med*. 2018;6(3):191-192. doi:10.16048/j.issn.2095-5561.2018.03.26

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