CEN Case Reports (2024) 13:143–144
https://doi.org/10.1007/s13730-023-00817-3

LETTER TO THE EDITOR(AUTHOR'S REPLY)

Author's reply to "Immune complex-mediated glomerulonephritis with ANCA positivity: what should nephrologists consider?"

Masaki Ueno[1] · Sawako Kobayashi[2] · Shinichiro Asakawa[1] · Shigeyuki Arai[1] · Michito Nagura[1] · Osamu Yamazaki[1] · Yoshifuru Tamura[1] · Ryuji Ohashi[3] · Shigeru Shibata[1] · Yoshihide Fujigaki[1]

Received: 19 July 2023 / Accepted: 15 August 2023 / Published online: 1 September 2023

We would like to express our gratitude to Dr. Taniguchi for showing interest in our case report [1] and providing valuable comments on the diagnostic aspects of our case.

Dr. Taniguchi suggested that the glomerular pathology in our case cannot be explained by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) due to the presence of immune complex-mediated glomerulonephritis instead of ANCA-associated glomerulonephritis.

ANCA-associated glomerulonephritis is characterized by pauci-immune necrotizing glomerulonephritis, which is pathologically defined by mild or absent staining of immunoglobulins and/or complement in the glomerular tuft through immunofluorescence, as well as few or no electron-dense deposits (EDDs) observed via electron microscopy [2]. In our patient's kidney biopsy, out of the 24 glomeruli, we identified 2 globally sclerotic glomeruli. In the non-sclerotic glomeruli, we observed three glomeruli with cellular crescents, exudation of fibrin-like material, and inflammatory cell infiltration in the intra- and extra-glomerular capillary area. Only half of the glomeruli showed a mild increase in mesangial cells and matrix, making the diagnosis of mesangial proliferative glomerulonephritis less likely. In patients with ANCA-associated crescentic glomerulonephritis, 50% of biopsies with deposits on electron microscopy and 14% of those without deposits usually showed mild mesangial hypercellularity [3].

Immunofluorescence staining in our patient revealed weakly positive results for IgA, IgG, IgM, C3, κ, and λ light chains in the mesangial areas, but negative for C1q. These findings did not suggest IgA nephropathy or IgA-dominant infectious glomerulonephritis. There is growing evidence supporting the involvement of complement alternative pathway activation in both granulomatosis with polyangiitis and microscopic polyangiitis [4]. Previous reports have documented that approximately 60% of AAV patients exhibit mild deposits of immunoglobulins and/or complement components in the glomerular tuft and/or in mesangial area on renal biopsies [3, 5, 6].

Electron microscopy of our patient revealed EDDs only in the mesangial areas, partial foot process effacement, and irregular thickening of the glomerular basement membrane. Marked platelet accumulation was found in the capillary lumen, and some platelets appeared to be in contact with endothelial cells. Infiltration of mononuclear cells and polymorphonuclear cells, as well as fibrin deposition within the glomerular capillary lumina, were also observed, suggesting the presence of glomerular capillaritis. The distribution of EDDs did not indicate postinfectious glomerulonephritis or IgA-dominant infectious glomerulonephritis. Electron microscopy has shown substantial EDDs in over half of renal biopsies from patients with ANCA-associated crescentic glomerulonephritis, with moderate numbers of mesangial deposits observed in nearly half of these cases [3].

Therefore, we believe that the glomerular pathology in our case aligns with the definition of pauci-immune necrotizing glomerulonephritis. Although the number of crescents formed in our case is low, it is known that the early phase of ANCA-associated glomerulonephritis does not necessarily show glomerular crescents in more than 50% of glomeruli. While proteinase 3 (PR3)-ANCA-associated glomerulonephritis is less common in Japan, and PR3-ANCA can be generated as an innocent bystander in various conditions such as infection and autoimmune abnormalities, we diagnosed our case as renal limited PR3-ANCA-associated glomerulonephritis.

✉ Yoshihide Fujigaki
fujigaki@med.teikyo-u.ac.jp

[1] Department of Internal Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo, Japan

[2] Division of Nephrology, Tokyo-Kita Medical Center, Kita-ku, Tokyo, Japan

[3] Department of Integrated Diagnostic Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan

Our patient exhibited positive circulating immune complexes and low serum C4, which became negative and normalized, respectively, soon after corticosteroid therapy. It is worth mentioning that cryoglobulin was also detected in our patient, suggesting that cryoglobulin may have contributed to the low C4 level. However, it has been reported that circulating immune complexes can be found in patients with AAV [7, 8]. These immune complexes are believed to be transient and likely cleared quickly in AAV [9]. However, unlike the frequency of low serum C3 levels, only a small number of AAV patients present with low C4 levels at diagnosis [10, 11]. This observation suggests the possible involvement of the classical pathway activation.

In conclusion, our patient experienced the emergence of PR3-ANCA-associated glomerulonephritis with mesangial immune deposition during the clinical course of IgG λ monoclonal gammopathy of uncertain significance. The patient's clinical symptoms, including slight appetite loss, fatigue, and slight anemia, along with nephritic urinalysis, positive C-reactive protein, and PR3-ANCA, are all consistent with AAV and ANCA-associated glomerulonephritis. These symptoms were normalized relatively soon after corticosteroid therapy. However, the pathophysiological roles of immune complex formation and complement activation in patients with ANCA-associated glomerulonephritis still need to be elucidated.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

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

Informed consent Written informed consent was obtained from the patient.

References

1. Ueno M, Kobayashi S, Asakawa S, Arai S, Nagura M, Yamazaki O, Tamura Y, Ohashi R, Shibata S, Fujigaki Y. Emergence of proteinase 3-antineutrophil cytoplasmic antibody-associated glomerulonephritis with mesangial immune deposition during the clinical course of IgG λ monoclonal gammopathy of uncertain significance. CEN Case Rep. 2023;11(4):463–70.
2. Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int. 2003;63(3):1164–77.
3. Haas M, Eustace JA. Immune complex deposits in ANCA-associated crescentic glomerulonephritis: a study of 126 cases. Kidney Int. 2004;65(6):2145–52.
4. Chen M, Jayne DRW, Zhao M-H. Complement in ANCA-associated vasculitis: mechanisms and implications for management. Nat Rev Nephrol. 2017;13(6):359–67.
5. Yu F, Chen M, Wang S-X, Zou W-Z, Zhao M-H, Wang H-Y. Clinical and pathological characteristics and outcomes of Chinese patients with primary anti-neutrophil cytoplasmic antibodies-associated systemic vasculitis with immune complex deposition in kidney. Nephrology. 2007;12(1):74–80.
6. Hirose O, Itabashi M, Takei T, Honda K, Nitta K. Antineutrophil cytoplasmic antibody-associated glomerulonephritis with immunoglobulin deposition. Clin Exp Nephrol. 2017;21(4):643–50.
7. Howell SB, Epstein WV. Circulating immunoglobulin complexes in Wegener's granulomatosis. Am J Med. 1976;60(2):259–68.
8. Sølling J. Circulating immune complexes in glomerulonephritis: a longitudinal study. Clin Nephrol. 1983;20(4):177–89.
9. Ronco P, Verroust P, Mignon F, et al. Immunopathological studies of polyarteritis nodosa and Wegener's granulomatosis: a report of 43 patients with 51 renal biopsies. Q J Med. 1983;52(206):212–23.
10. Molad Y, Tovar A, Ofer-Shiber S. Association of low serum complement C3 with reduced patient and renal survival in antimyeloperoxidase-associated small-vessel vasculitis. Nephron Clin Pract. 2014;126(1):67–74.
11. Manenti L, Vaglio A, Gnappi E, Maggiore U, Allegri L, Allinovi M, et al. Association of serum C3 concentration and histologic signs of thrombotic microangiopathy with outcomes among patients with ANCA-associated renal vasculitis. Clin J Am Soc Nephrol. 2015;10(12):2143–51.