IN VIVO *39*: 1731-1738 (2025)
doi: 10.21873/invivo.13975

IgA Nephropathy Associated With Infliximab Treatment in Patients With Crohn's Disease: Study of IgA1 and IgA2 Expression in Glomeruli

AKIRA MIMA, TAKAHIRO NAKAMOTO, TAKAMASA MATSUKI, SUGURU KIDO, YUTA SAITO, TAKAAKI MORIKAWA, KEISHI MATSUMOTO, HIDEMASA GOTODA and SHINJI LEE

Department of Nephrology, Osaka Medical and Pharmaceutical University, Osaka, Japan

Abstract

Background/Aim: It is well known that infliximab is an anti-tumor necrosis factor chimeric factor that is effective in treating inflammatory bowel diseases, such as Crohn's disease. Recently, there have been reports of new onset or flare-ups of immunoglobulin A (IgA) nephropathy during infliximab therapy for Crohn's disease. Inflammatory bowel disease-associated IgA nephropathy has been associated with IgA2; However, its activation by infliximab is still unknown.
Case Report: We report our experience with two patients who experienced acute exacerbations of pre-existing abnormal urinalysis and renal dysfunction 1-18 years following infliximab treatment for Crohn's disease. Renal biopsies at the time of renal disease flare-up revealed IgA nephropathy in one patient and mesangial proliferative nephropathy in the other. Immunostaining results showed no clear predominance of intraglomerular expression of IgA2, and the patient diagnosed with IgA nephropathy entered remission with high dose methylprednisolone pulse therapy and oral corticosteroids, without the need for tonsillectomy. In contrast, the patient with mesangial proliferative nephritis had many devastated glomeruli, thus corticosteroids were not administrated, and the patient was followed up.
Conclusion: The clinical course of our patients, along with similar cases reported in the literature, indicates that infliximab therapy for Crohn's disease is linked to a relatively high risk of new-onset IgA nephropathy or disease relapse. This report is notable because it is the first to compare the expression of IgA1 and IgA2 in glomeruli in nephritis associated with infliximab therapy.

Keywords: IgA nephropathy, infliximab, Crohn's disease, IgA1, IgA2.

Introduction

Immunoglobulin A (IgA) nephropathy is one of the most common forms of chronic glomerulonephritis, and it has been demonstrated to occur in association with inflammatory bowel disease (IBD) (1). Crohn's disease is a representative IBD, and several previous reports have shown that IgA nephropathy can be associated with

Akira Mima, MD, Ph.D., Department of Nephrology, Osaka Medical and Pharmaceutical University, Osaka, 569-8686, Japan. Tel: +81 726831221, e-mail: akira.mima@ompu.ac.jp

Received February 24, 2025 | Revised March 8, 2025 | Accepted March 10, 2025

Crohn's disease. Several cytokines are involved in the pathogenesis of Crohn's disease, with tumor necrosis factor-alpha (TNF-α) playing a particularly crucial role (2). Therefore, infliximab, an antibody targeting TNF-α, is a proven and well-established treatment for Crohn's disease. With the long-term use of infliximab therapy, a range of adverse events has emerged. Among these, the new onset or worsening of previously-diagnosed IgA nephropathy has been reported, with Crohn's disease being more commonly associated than ulcerative colitis (3).

Although IgA2 may be involved in IgA nephropathy associated with IBD, as IgA2 is the predominant IgA subtype in the colon, IgA1 appears to be more involved in the pathogenesis (4). Since the distribution of IgA1 and IgA2 subtypes within the glomerulus in IgA nephropathy associated with infliximab treatment has never been reported before, this study is the first to clarify this point.

Table I. *Clinical data of case 1.*

Laboratory data		Reference values
Hemoglobin	11.0	13.0-16.6 (g/dl)
Hematocrit	30.6	40-50 (10^4/μl)
BUN	31	8-20 (mg/dl)
Creatinine	2.38	0.65-1.09 (mg/dl)
Na	142	137-147 (mEq/l)
K	4.3	3.5-5.0 (mEq/l)
IgG	1,334	870-1,700 (mg/dl)
IgA	618	110-410 (mg/dl)
IgM	115	33-190 (mg/dl)
C3	120	80-140 (mg/dl)
C4	27	11-34 (mg/dl)
Urinalysis		
Urinary protein (g/g creatinine)	0.88	<0.15
Urinary sediment examination		
Red blood cell	84	<20 μl
Red blood cell casts	1	None

BUN: Blood urea nitrogen; Na: sodium; K: potassium; IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; C3: complement C3; C4: complement C4.

Case Report

Patients and ethics. All procedures involving human participants in this study were conducted in line with the ethical standards set by the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical guidelines. Written informed consent, including consent for publication, was obtained from the patients. As the study involved fewer than nine patients, an ethical review was not necessary according to the institution's guidelines (Osaka Medical and Pharmaceutical University). Data were collected and analyzed retrospectively using electronic medical records managed by the Department of Nephrology at Osaka Medical and Pharmaceutical University Hospital. Data on age, sex, laboratory data, and specific treatment for IgA nephropathy were obtained from the electronic medical records and kidney biopsy database.

Kidney biopsy and immunohistochemical staining. Kidney specimens were obtained using a 16-gauge biopsy needle (Boston Scientific, Boston, MA, USA). Specimens were fixed in 10% formalin for the staining with Periodic acid-Schiff stains (PAS) and fixed in 2% glutaraldehyde for electron microscopy. Pathological data were obtained from kidney biopsy database. Immunohistochemical staining was performed with antibodies specific to IgA1(Santa-Cruz, Dallas, TX, USA) and IgA2 (Abcam, Cambridge, UK) using an established avidin-biotin detection method (Roche, Indianapolis, IN, USA).

Case 1. A 47-year-old Japanese man was referred to our hospital with increased levels of serum creatine, proteinuria, and microscopic hematuria. He had Crohn's disease for 20 years, had been on infliximab for 18 years, and his Crohn's disease was in remission. His past medical history included hypertension, hyperuricemia, fatty liver, and sleep apnea syndrome. His family history was negative. The physical examination revealed a soft, non-tender abdomen, with no palpable spleen, liver, or kidneys. When he was admitted, he was afebrile. Table I indicates the clinical data on admission. Upon admission, the urinalysis indicated proteinuria of 0.88 g/g creatinine (urine protein-to-creatinine ratio) and dysmorphic microscopic hematuria. A renal biopsy was performed for possible chronic glomerulonephritis. Light microscopy

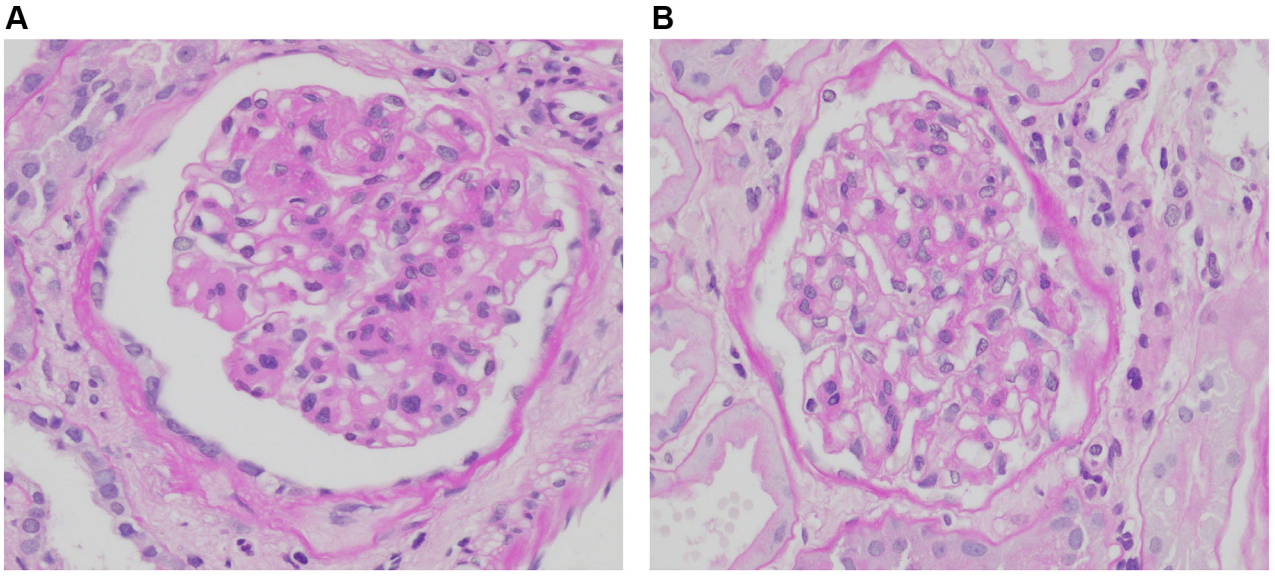

Figure 1. *Microscopy findings of the renal biopsy. Increase in mesangial cells and mesangial expansion are present. (A) Case 1, (B) Case 2, Periodic acid-Schiff staining was shown. Original magnification ×400.*

revealed increases in mesangial cells and mesangial expansion in periodic acid-Schiff staining (Figure 1A). Immunofluorescence showed deposits of IgG (–), IgA (1+), IgM (±), C3 (1+), C1q (–) in mesangial lesions (Figure 2A). Electron microscope study revealed high electron density deposits in the mesangial area, leading to the diagnosis of IgA nephropathy (Figure 3A). Immunohistochemistry of IgA1 and IgA2 showed similar levels of expression in the glomeruli (Figure 4A).

Case 2. A 48-year-old Japanese man was referred to our hospital due to an increase in serum creatine and microscopic hematuria. He had undergone surgery for hemorrhoids 22 years ago and had intractable diarrhea for the past 14 years. One year ago, a perianal abscess was observed, and after close examination, Crohn's disease was diagnosed, and infliximab treatment was started. After treatment, his Crohn's disease was in remission.

His past medical history was glaucoma. His family history was negative. The physical examination revealed a soft, non-tender abdomen, with no palpable spleen, liver, or kidneys. When he was admitted, he was afebrile. Table II indicates the clinical data on admission. Upon admission, the urinalysis indicated proteinuria of 0.13 g/g creatinine (urine protein-to-creatinine ratio) and dysmorphic microscopic hematuria. A renal biopsy was performed for possible

Table II. *Clinical data of case 2.*

Laboratory data		Reference values
Hemoglobin	15.3	13.0-16.6 (g/dl)
Hematocrit	43.5	40-50 (104/ml)
BUN	16	8-20 (mg/dl)
Creatinine	1.14	0.65-1.09 (mg/dl)
Na	141	137-147 (mEq/l)
K	4.4	3.5-5.0 (mEq/l)
IgG	1,661	870-1,700 (mg/dl)
IgA	212	110-410 (mg/dl)
IgM	75	33-190 (mg/dl)
C3	82	80-140 (mg/dl)
C4	11	11-34 (mg/dl)
Urinalysis		
Urinary protein (g/g creatinine)	0.13	<0.15
Urinary sediment examination		
Red blood cell	33	<20 µl

BUN: Blood urea nitrogen; Na: sodium; K: potassium; IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; C3: complement C3; C4: complement C4.

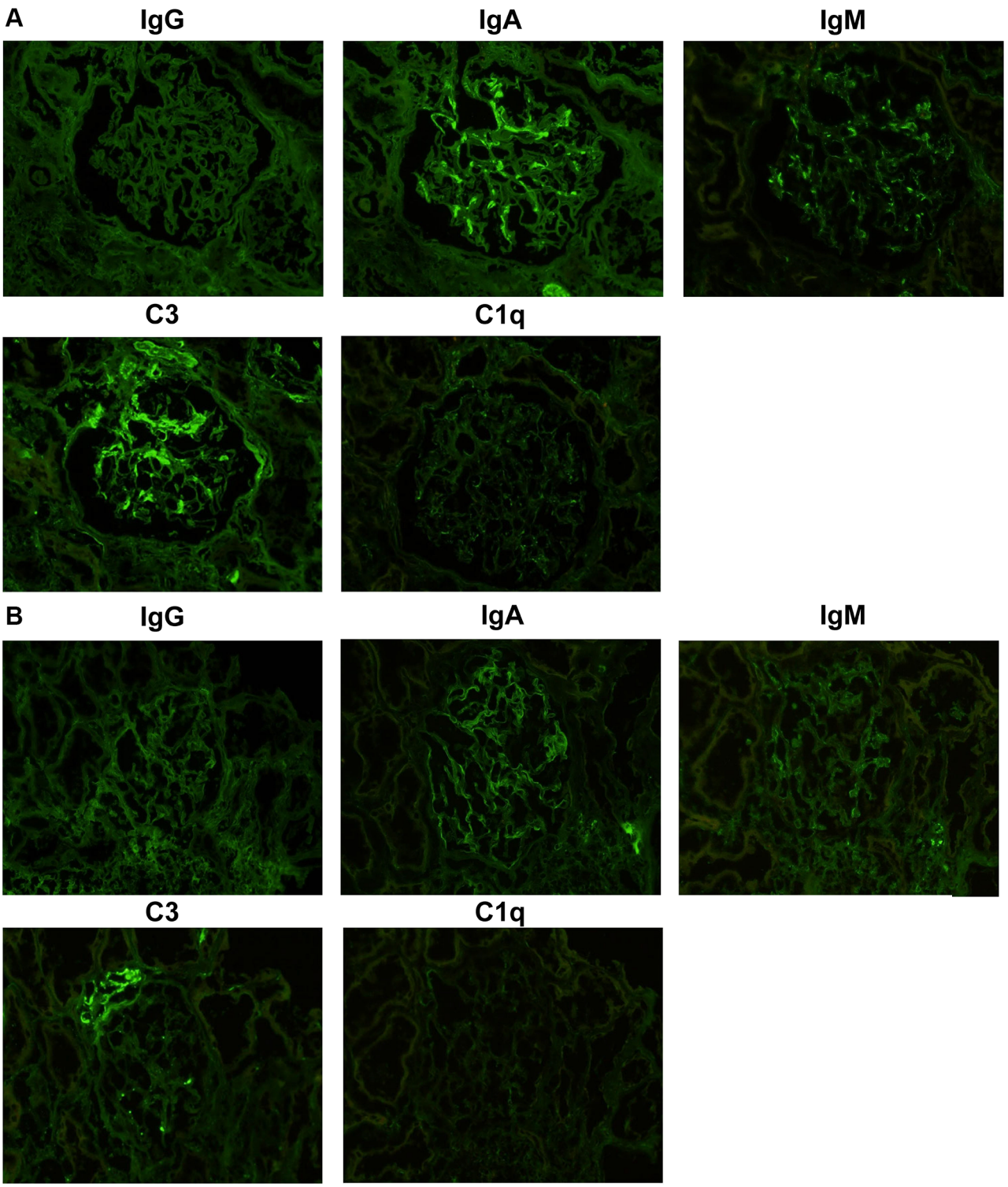

Figure 2. *Immunofluorescence staining of the kidney biopsy. (A) Case 1: IgG (–), IgA (1+), IgM (±), C3 (1+), and C1q (–) dominant in mesangial lesions (original magnification ×400). (B) Case 2: IgG (±), IgA (1+), IgM (±), C3 (–), and C1q (–) dominant in mesangial lesions (original magnification ×400).*

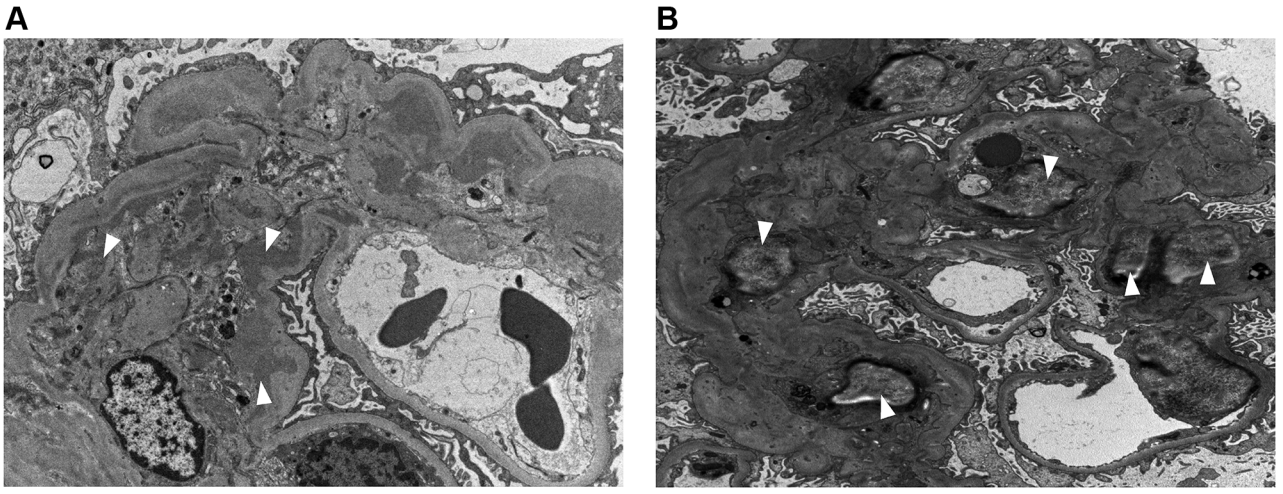

Figure 3. *Electron microscopy. (A) Case 1: High electron density deposits in the mesangial area (arrowheads) (original magnification ×4,000). (B) Case 2: Electron microscopy revealed mesangial cell proliferation (arrowheads) (original magnification ×4,000).*

chronic glomerulonephritis. Light microscopy revealed increases in mesangial cells and mesangial expansion in periodic acid-Schiff staining (Figure 1B). Immunofluorescence showed deposits of IgG (±), IgA (1+), IgM (±), C3 (–), C1q (–) in mesangial lesions (Figure 2B). Electron microscopy revealed mesangial cell proliferation, but the high electron-density deposits in the mesangial area were unclear, leading to the diagnosis of mesangial proliferative glomerulonephritis (Figure 3B). Immunohistochemistry revealed that IgA1 was predominantly stained positive over IgA2 in the mesangial area (Figure 4B).

Discussion

Recently, a retrospective case-control study reported an increased prevalence of inflammatory bowel disease (IBD) in patients with IgA nephropathy (5). Additionally, in a review of 23 patients with both Crohn's disease and IgA nephropathy, 17 were diagnosed with both conditions simultaneously (6). Among these patients, 50% of patients progressed to end-stage renal disease, while 25% of patients with primary IgA nephropathy reached the same stage (7). However, it remains unclear whether the activity of IgA nephropathy is linked to the activity of inflammatory bowel disease. In a study of patients with active IgA nephropathy, around 25% of patients with Crohn's disease exhibited signs of active inflammatory bowel disease (IBD), while no ulcerative colitis patients showed signs of active inflammation (8). Population-based cohort studies in Sweden have found that patients with IgA nephropathy are at an increased risk of developing IBD both prior to and following the diagnosis of kidney disease (9). Furthermore, studies have identified risk loci associated with genes involved in intestinal mucosal integrity and have discovered common risk alleles for both IgA nephropathy and IBD (10).

The gut microbiome induces B cell activation through B cell-activating factors, and this overstimulation leads to a significant shift from IgA2 to IgA1 production (11). Additionally, abnormal O-linked glycosylation of IgA has been observed in patients with Crohn's disease (12). Indeed, in this study, the expression of IgA1 in the glomerulus was higher than that of IgA2.

More than 90% of serum IgA is IgA1 and plasma cells derived from nasopharynx-associated lymphoid tissue (NALT) produce mainly IgA1, while plasma cells derived from gastrointestinal-associated lymphoid tissue (GALT) produce equal amounts of IgA1 and IgA2 (13). The fact that genes involved in intestinal immunity were listed as candidate genes for the development of IgA nephropathy

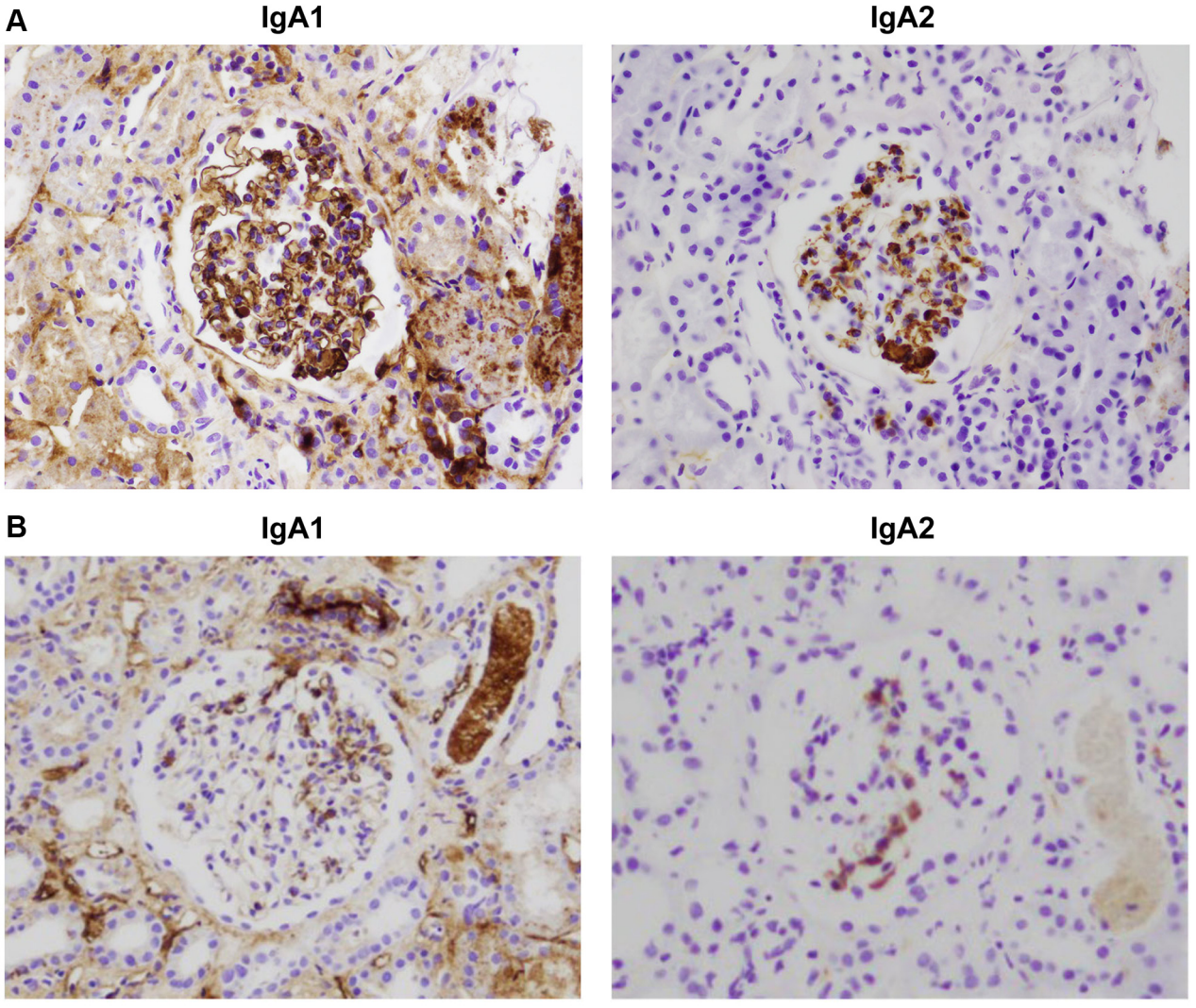

Figure 4. *Immunohistochemical analysis for IgA1 and IgA2 in kidney biopsy samples. (A) Case 1, (B) Case 2, representative immunohistochemistry of IgA1 and IgA2.*

and the lack of efficacy of tonsillectomy therapy suggests that gastrointestinal tract-associated lymphoid tissue (GALT) is also involved in the development of IgA nephropathy (14). This is supported by the favorable results reported in trials using intestinal selective steroids in patients with IgA nephropathy (15).

An apoptosis inhibitor of macrophages and abnormal T cells may also contribute to the pathogenesis of IgA nephropathy. The disease is typically characterized by a higher proportion of Th2 cells and a lower proportion of Th1 cells (16). Interleukin (IL)-4 is secreted by Th2 cells and stimulates B cells to produce antibodies (17). Interestingly, it has been shown that alpha-hemolytic streptococcal stimulation of tonsillar mononuclear cells isolated from IgA nephropathy patients increased interferon (IFN)-γ and IL-4 concentrations in the culture medium (18).

Several cytokines including TNF-α plays a significant role in developing chronic kidney disease and is an important component of the Th1 cytokine cascade (19, 20). Therefore, chronic inhibition of TNF-α may induce a

Th2 dominant status. It has been reported that the combination of corticosteroid therapy and tonsillectomy effectively reduces renal dysfunction and is well tolerated without worsening Crohn's disease (17).

Conclusion

We report two cases of IgA nephropathy and mesangial proliferative glomerulonephritis that developed after infliximab treatment for Crohn's disease. The results of the immunostaining analyses of the glomeruli did not clearly demonstrate a predominance of IgA2 expression.

Conflicts of Interest

A. Mima received a speaker's honorarium from Torii, Bayer, Eli Lilly, Mochida, and Boehringer Ingelheim. A. Mima received research grants from Chugai, Sumitomo Pharma, and Torii.

Authors' Contributions

All Authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Conceptualization, A.M., T.N., and T.M.; Methodology, S.K.; Software, A.M. and Y.S.; Validation, T.M., and K.M.; Formal Analysis, A.M.; Investigation, H.G.; Resources, S.L.; Data Curation, A.M.; Writing – Original Draft Preparation, A.M.; Writing – Review & Editing, A.M.; Visualization, S.L.; Supervision, S.L.; Project Administration, A.M.; Funding Acquisition, A.M.

Acknowledgements

The Authors thank Dr. Yoshinobu Hirose and Dr. Tatsuhiko Mori (Osaka Medical and Pharmaceutical University) for the discussions on the pathology. During the preparation of this publication, the authors used DeepL and ChatGPT for proofreading. After using this tool, the Authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding

This work was supported by JSPS KAKENHI Grant Number 22K08368 (to A. Mima) and Osaka Kidney Foundation (OKF24-0002).

References

1 Saha MK, Julian BA, Novak J, Rizk DV: Secondary IgA nephropathy. Kidney Int 94(4): 674-681, 2018. DOI: 10.1016/j.kint.2018.02.030
2 Awad AS, You H, Gao T, Cooper TK, Nedospasov SA, Vacher J, Wilkinson PF, Farrell FX, Brian Reeves W: Macrophage-derived tumor necrosis factor-α mediates diabetic renal injury. Kidney Int 88(4): 722-733, 2015. DOI: 10.1038/ki.2015.162
3 Corica D, Romano C: Renal involvement in inflammatory bowel diseases. J Crohns Colitis 10(2): 226-235, 2016. DOI: 10.1093/ecco-jcc/jjv138
4 Gleeson PJ, Camara NOS, Launay P, Lehuen A, Monteiro RC: Immunoglobulin A antibodies: from protection to harmful roles. Immunol Rev 328(1): 171-191, 2024. DOI: 10.1111/imr.13424
5 Yandian F, Caravaca-Fontán F, Herrera Hernandez LP, Soler MJ, Sethi S, Fervenza FC: Kidney diseases associated with inflammatory bowel disease: impact of chronic histologic damage, treatments, and outcomes. Kidney Int Rep 9(2): 383-394, 2023. DOI: 10.1016/j.ekir.2023.11.011
6 Tamura H: IgA nephropathy associated with Crohn's disease. World J Methodol 13(3): 67-78, 2023. DOI: 10.5662/wjm.v13.i3.67
7 Joher N, Gosset C, Guerrot D, Pillebout E, Hummel A, Boffa JJ, Faguer S, Rabant M, Higgins S, Moktefi A, Delmas Y, Karras A, Lapidus N, Amiot A, Audard V, El Karoui K: Immunoglobulin A nephropathy in association with inflammatory bowel diseases: results from a national study and systematic literature review. Nephrol Dial Transplant 37(3): 531-539, 2022. DOI: 10.1093/ndt/gfaa378
8 Yu HH, Chiang BL: Diagnosis and classification of IgA nephropathy. Autoimmun Rev 13(4-5): 556-559, 2014. DOI: 10.1016/j.autrev.2014.01.030
9 Rehnberg J, Symreng A, Ludvigsson JF, Emilsson L: Inflammatory bowel disease is more common in patients with IgA nephropathy and predicts progression of ESKD: a Swedish population-based cohort study. J Am Soc Nephrol 32(2): 411-423, 2021. DOI: 10.1681/ASN.2020060848
10 Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, Fasel D, Lata S, Prakash S, Shapiro S, Fischman C, Snyder

HJ, Appel G, Izzi C, Viola BF, Dallera N, Del Vecchio L, Barlassina C, Salvi E, Bertinetto FE, Amoroso A, Savoldi S, Rocchietti M, Amore A, Peruzzi L, Coppo R, Salvadori M, Ravani P, Magistroni R, Ghiggeri GM, Caridi G, Bodria M, Lugani F, Allegri L, Delsante M, Maiorana M, Magnano A, Frasca G, Boer E, Boscutti G, Ponticelli C, Mignani R, Marcantoni C, Di Landro D, Santoro D, Pani A, Polci R, Feriozzi S, Chicca S, Galliani M, Gigante M, Gesualdo L, Zamboli P, Battaglia GG, Garozzo M, Maixnerová D, Tesar V, Eitner F, Rauen T, Floege J, Kovacs T, Nagy J, Mucha K, Pączek L, Zaniew M, Mizerska-Wasiak M, Roszkowska-Blaim M, Pawlaczyk K, Gale D, Barratt J, Thibaudin L, Berthoux F, Canaud G, Boland A, Metzger M, Panzer U, Suzuki H, Goto S, Narita I, Caliskan Y, Xie J, Hou P, Chen N, Zhang H, Wyatt RJ, Novak J, Julian BA, Feehally J, Stengel B, Cusi D, Lifton RP, Gharavi AG: Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet 46(11): 1187-1196, 2014. DOI: 10.1038/ng.3118

11 Cerutti A: The regulation of IgA class switching. Nat Rev Immunol 8(6): 421-434, 2008. DOI: 10.1038/nri2322

12 Larson C, Munir N, Rao P, Farkash E, Kathuria P, Romain D, Berinstein J: Crohn's disease associated with IgA nephropathy effectively treated with the interleukin-23 inhibitor risankizumab. ACG Case Rep J 11(7): e01437, 2024. DOI: 10.14309/crj.0000000000001437

13 Gesualdo L, Di Leo V, Coppo R: The mucosal immune system and IgA nephropathy. Semin Immunopathol 43(5): 657-668, 2021. DOI: 10.1007/s00281-021-00871-y

14 Zhou X, Wu Y, Zhu Z, Lu C, Zhang C, Zeng L, Xie F, Zhang L, Zhou F: Mucosal immune response in biology, disease prevention and treatment. Signal Transduct Target Ther 10(1): 7, 2025. DOI: 10.1038/s41392-024-02043-4

15 Coppo R: Corticosteroids in IgA nephropathy: lessons from recent studies. J Am Soc Nephrol 28(1): 25-33, 2017. DOI: 10.1681/ASN.2016060647

16 Ruszkowski J, Lisowska KA, Pindel M, Heleniak Z, Dębska-Ślizień A, Witkowski JM: T cells in IgA nephropathy: role in pathogenesis, clinical significance and potential therapeutic target. Clin Exp Nephrol 23(3): 291-303, 2019. DOI: 10.1007/s10157-018-1665-0

17 Shimizu A, Tsuboi N, Haruhara K, Shirai I, Ogawa K, Miura A, Oshiro K, Ueda H, Yokote S, Okabe M, Sasaki T, Ikeda M, Yokoo T: Active flare of IgA nephropathy during long-term therapy with anti-tumor necrosis factor-α antibody drugs for Crohn's disease: three case reports and literature review. CEN Case Rep 13(4): 249-257, 2024. DOI: 10.1007/s13730-023-00836-0

18 Chen X, Liu H, Peng Y, He L, Zhang Y, Xie Y, Peng X, Liu C, Liu F: Expression and correlation analysis of IL-4, IFN-gamma and fcalphari in tonsillar mononuclear cells in patients with iga nephropathy. Cell Immunol 289(1-2): 70-75, 2014. DOI: 10.1016/j.cellimm.2014.03.004

19 Yasuzawa T, Nakamura T, Ueshima S, Mima A: Protective effects of eicosapentaenoic acid on the glomerular endothelium *via* inhibition of EndMT in diabetes. J Diabetes Res 2021: 2182225, 2021. DOI: 10.1155/2021/2182225

20 Mima A, Yasuzawa T, King GL, Ueshima S: Obesity-associated glomerular inflammation increases albuminuria without renal histological changes. FEBS Open Bio 8(4): 664-670, 2018. DOI: 10.1002/2211-5463.12400