Case Report

A Case of IgA Nephropathy with Membranoproliferative Glomerulonephritis-like Features

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Abstract

A 73-year-old man was referred due to the onset of nephrotic-range proteinuria. He had been diagnosed with rheumatoid arthritis 18 years prior and had achieved remission with treatment, including methotrexate and janus kinase (JAK) inhibitors. Although routine follow-ups had not revealed any urinary abnormalities, subsequent tests detected proteinuria and hematuria in the absence of infection or other symptoms. As the urinary abnormalities persisted, with a serum albumin decrease and proteinuria measuring 5.7 g/day, indicating nephrotic syndrome, the patient was referred to our hospital for further evaluation, and a renal biopsy was performed. Light microscopy revealed mesangial cell proliferation, endocapillary proliferation, and double-contoured basement membranes. Immunofluorescence microscopy showed IgA-dominant deposits in both mesangial areas and capillary walls. Transmission electron microscopy demonstrated electron-dense deposits in the mesangium and subendothelial, regions, leading to the diagnosis of membranoproliferative glomerulonephritis (MPGN)-type IgA nephropathy. Immunostaining with the Gd-IgA1 (galactose deficient IgA1)-specific antibody (KM55) was positive, consistent with the diagnosis. Following the initiation of steroid therapy, proteinuria rapidly decreased,

achieving complete remission within 5 months. IgA nephropathy with MPGN-like features often presents as nephrotic syndrome, differing from the typical pathological and clinical presentation of IgA nephropathy, making differentiation from secondary MPGN and other conditions sometimes challenging. This case suggests that KM55 staining may offer an additional information in differentiating atypical IgA nephropathy with non-classical pathological features.

Keyword: IgA nephropathy, membranoproliferative glomerulonephritis, Gd-IgA1, nephrotic syndrome, rheumatoid arthritis.

Introduction

IgA nephropathy (IgAN) is the most prevalent common primary glomerulonephritis worldwide[1]. In adults, IgAN typically presents as asymptomatic hematuria accompanied by mild to moderate proteinuria, whereas nephrotic syndrome is an uncommon manifestation. A definitive diagnosis is established through renal biopsy. The hallmark finding is the mesangial deposition of IgA as the predominant or co-dominant immunoglobulin, confirmed by immunofluorescence microscopy. Light microscopy typically reveals mesangial proliferation, which may be accompanied by increased mesangial matrix, focal or diffuse endocapillary hypercellularity, and, in severe cases, crescent formation or global glomerulosclerosis[2]. Electron microscopy often identifies electron-dense deposits within the mesangium and para-mesangium, with occasional subendothelial or subepithelial involvement. In rare cases, IgAN can exhibit membranoproliferative glomerulonephritis (MPGN)-like pathological features, making differentiation from other conditions such as IgA-dominant MPGN challenging[3]. This report describes a unique case of IgAN presenting with MPGN-like pathological features, where the use of galactose-deficient IgA1 (Gd-IgA1)-specific antibody (KM55) staining offered the additional information,

highlighting its utility as a diagnostic tool for atypical presentations of IgAN.

Case Report

A 73-year-old man was referred due to the onset of nephrotic-range proteinuria. He had been diagnosed with rheumatoid arthritis (RA) 18 years prior and has been in remission with treatment, including methotrexate and tofacitinib, a janus kinase (JAK) inhibitor. He had a history of type 2 diabetes, for which he had been on insulin therapy for the past 19 years, with HbA1c levels consistently maintained around 6.5-7.0%. Although no urinary abnormalities were observed during routine follow-up, proteinuria and hematuria were subsequently detected in the absence of infection or symptoms. The urinary abnormalities persisted, and with a serum albumin decrease and proteinuria of 5.7 g/day indicating nephrotic syndrome, resulting in the consultation to our hospital, leading to a renal biopsy. There was no family history of kidney diseases.

On admission, the patient was on methotrexate (14 mg/week), tofacitinib (10 mg/day) and iguratimod (50 mg/day) for RA management. The patient's body temperature was 36.5°C, pulse rate was 90 per minute, and blood pressure was 114/75 mmHg. The patient exhibited normal heart sounds without murmurs, clear

lung sounds and no evidence of purpura, but mild bilateral pitting edema was observed in the lower extremities. The urinalysis showed proteinuria (4+) (quantitated at 5.25 g/gCr) and occult blood (3+). Urine microscopy showed red blood cells (100 ≥ per high power field, dysmorphic). Laboratory examination revealed an elevated levels of serum IgA (s-IgA, 547.0 mg/dL) with normal levels of IgG and IgM, and low levels of serum total protein (6.2 g/dL) and serum albumin (2.9 g/dL). The levels of serum creatinine (s-Cr) was 1.0 mg/dL, estimated glomerular filtration rate (eGFR) was 56.6 ml/min/1.73m^2 and HbA1c was 7.4%. Serum and urine analysis did not indicate monoclonal gammopathy. Serum complement levels were normal. Hepatitis B surface antigen and hepatitis C antibody test results were negative. The patient was positive for rheumatoid factor but negative for anti-nuclear antibodies, anti-neutrophil cytoplasmic, anti-glomerular basement membrane, anti-DNA antibodies and cryoglobulin. Chest and abdomen computed tomography revealed no abnormal findings. A renal biopsy was performed to determine the pathological characteristics. Light microscopy revealed mesangial cell proliferation, endocapillary proliferation, and double-contoured basement membranes (Figure 1). Immunofluorescence microscopy showed IgA-dominant deposits in both the mesangial areas and

capillary walls (Figure 1). Transmission electron microscopy demonstrated electron-dense deposits in the mesangium, subendothelialium, and, to a lesser extent, subepithelial regions, with evidence of mesangial interposition (Figure 1), leading to the diagnosis of membranoproliferative glomerulonephritis (MPGN)-type IgA nephropathy. Additionally, Immunofluorescence staining with the Gd-IgA1-specific antibody (KM55, Immuno-Biological Laboratories; #10777) was positive (Figure 2), consistent with the diagnosis of MPGN-type IgA nephropathy. Following the diagnosis, oral prednisolone at 40 mg/day (0.6 mg/kg) was initiated (Figure 3). The patient's proteinuria levels gradually decreased, leading to the complete remission in 5 months. The prednisolone dose was tapered to 10 mg/day over 6 months.

DISCUSSION

We experienced a case of IgAN with MPGN-like pathological features, where KM55 staining offered the additional information. The typical pathological features of IgAN involve mesangial proliferative glomerulonephritis with immune complex deposition in the mesangial region. However, certain cases exhibit findings resembling MPGN, such as mesangial interposition with subendothelial dense

deposits or irregular, segmental subepithelial deposits under electron microscopy. Indeed, analysis of the Japan Renal Biopsy Registry (J-RBR) for 2009–2010 revealed that MPGN (types I and III) was reported in 9 out of 2,177 cases (0.4%) of IgAN[3]. These cases of MPGN-type IgAN are more frequently observed in children and are often associated with atypical clinical presentations, such as nephrotic syndrome[4, 5]. Additionally, a cohort study of 15 patients with non-hepatic IgA-dominant deposits and MPGN-like features reported that 27% progressed to end-stage renal disease, while 73% developed nephrotic syndrome over an average follow-up of three years[6]. Pathological conditions involving IgA-dominant MPGN include IgAN, IgA vasculitis, infection-associated nephropathy, hepatitis-associated nephropathy, inflammatory bowel disease-associated nephritis, and autoimmune conditions such as lupus nephritis or RA. Diagnosing these diseases can be sometimes challenging, particularly in differentiating IgA-dominant MPGN from MPGN-type IgAN. In this context, KM55 staining has emerged as a potentially valuable tool for providing additional diagnostic information.

The pathogenesis of IgAN is increasingly understood through the multi-hit hypothesis, where Gd-IgA1 plays a central role[7]. This model describes a cascade initiated by the overproduction of Gd-IgA1, followed by immune complex

formation and mesangial deposition, leading to nephritis. It is recently reported that staining of KM55, specifically targeting Gd-IgA1, provides diagnostic accuracy comparable to enzyme-linked immunosorbent assay (ELISA) measurements of Gd-IgA1[8]. It has also demonstrated utility in distinguishing between IgAN from other forms of nephritis, such as lupus nephritis or hepatitis C virus-associated nephropathy[9]. In studies of IgA-dominant infection-related glomerulonephritis, KM55 staining was negative or weakly positive in 11 out of 12 cases, with only one case showing strong positivity[10]. This highlights the potential of KM55 staining in distinguishing IgAN from IgA-dominant infection-related nephropathy. Furthermore, KM55 staining has been reported as negative in IgA-dominant MPGN[11]. In the present case of MPGN-type IgAN, KM55 staining was positive, reinforcing its utility in differentiating MPGN-type IgAN from IgA-dominant MPGN[11]. With recent advancements in treatments for IgAN, including B cell priming in the gut mucosa, the cytokines a proliferation-inducing ligand (APRIL), B-cell activating factor (BAFF), plasma cells, complement activation and endothelin pathway activation[12], accurate diagnosis has become increasingly important. The application of KM55 staining as a diagnostic aid holds promise for enhancing the precision of pathological evaluations and guiding clinical

management. In spite of its potential diagnostic power, several reports have indicated limitations of KM-55 staining. KM-55 positive staining has been reported not only in primary IgAN and IgA vasculitis, but also weakly in lupus nephritis, incidental IgA deposits and staphylococcal infection-associated glomerulonephritis, suggesting that positive KM-55 staining alone is not specific enough for a diagnosis of primary IgAN[13, 14].

Another important aspect is secondary IgAN. This condition is characterized by mesangial IgA deposition associated with systemic diseases or external factors, distinguishing it from primary IgAN. Common causes of secondary IgAN include autoimmune diseases such as RA and ankylosing spondylitis, as well as chronic liver diseases[15]. A study analyzing 100 cases of secondary IgAN, including those associated with liver disease (20 cases), RA (19 cases), ankylosing spondylitis (9 cases), Sjögren's syndrome (10 cases), and psoriasis (25 cases), revealed KM55 staining positivity in these cases with secondary IgAN[16], which is consistent with the similar findings, indicating KM-55 positive staining in both secondary and primary IgAN[14]. Collectively, these reports suggest that secondary and primary IgAN may share a common pathophysiology.. Although the patient had a long history of RA in the present case, the prolonged

quiescence of RA activity reduces the likelihood of secondary IgAN. As the possible drug-induced IgAN in this case, the patient's extended use (over seven years) of JAK inhibitors for RA treatment. To our knowledge, there has been only one report of IgA vasculitis associated with the JAK inhibitor, diagnosed based on the onset of symptoms after 6 months from the treatment and subsequent clinical improvement following drug discontinuation[17]. In our case, drug-induced IgA vasculitis due to JAK inhibitors seems to be unlikely, given the extended treatment duration and the absence of documented cases linking JAK inhibitors to IgAN. Currently, the JAK inhibitor has been discontinued following the initiation of steroid therapy. However, reintroduction of the JAK inhibitor is planned after tapering the prednisolone dosage, necessitating close monitoring of urinary findings during reintroduction. Recent literature highlights an increasing number of cases of drug-induced IgA N and IgA vasculitis associated with biologic agents, particularly TNF-α inhibitors[17-19]. These cases have been observed after both short- and long-term treatment durations. As the use of novel therapeutics expands, it is crucial to investigate their potential roles in the pathogenesis of IgAN.

In conclusion, KM55 staining may offer an additional information in

differentiating atypical IgA nephropathy, particularly in cases with atypical MPGN-like pathological features. Given the development of new treatments for IgAN, accurate diagnosis is essential for selecting the most appropriate therapeutic strategies. Further studies are necessary to evaluate the utility, sensitivity, and specificity of KM55 staining in the diagnosis of IgA nephropathy.

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Ethics statement: Informed consent was obtained from the participant included in the article.

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Figure Legends

Figure 1. Pathological findings of renal biopsy specimens.
(A-B) Immunofluorescence staining. Immunofluorescence staining of IgA (A) and C3 (B), showing both mesangial areas and capillary wall staining. (C-D) Light microscopic analysis. (C) Mesangial cell proliferation and endocapillary proliferation with Periodic acid-Schiff stain staining. (D) Double-contoured basement membranes with Periodic acid-Methenamine silver staining. (E-F) Transmission electron microscopy analysis. Transmission electron microscopy images, showing electron-dense deposits in mesangium (E) and subendothelialium with evidence of mesangial interposition (F).

Figure 2. Immunofluorescence findings of renal biopsy specimens for KM55.
Immunofluorescence staining of KM55 and IgA, showing both mesangial areas and capillary wall staining of KM55 and IgA.

Figure 3. Patient's clinical course.
MTX: Methotrexate, PSL: Prednisolone, U-TP: Urinary total protein, s-Cr: serum creatinine.

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