Immunotactoid glomerulonephritis in a patient with cold agglutinins: causal association or mere coincidence?

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Abstract

We report a case of immunotactoid glomerulonephritis (ITG) in a patient with cold agglutinins. An 86-year-old Japanese male with a history of hypertension, dyslipidemia, and gastric malignancy presented to our hospital for the evaluation of proteinuria and hematuria. He had an elevated blood pressure of 200/77 mmHg and edema of the lower extremities. Initial blood test results revealed an impaired renal function (creatinine, 1.37 mg/dL) and hypoalbuminemia (albumin, 2.6 g/dL). His estimated daily urinary protein was 5.89 g/g creatinine, meeting the diagnostic criteria for nephrotic syndrome. The selectivity index for proteinuria indicated low selectivity (0.329). We conducted a renal biopsy to identify the cause of nephrotic syndrome. Immunofluorescence microscopy demonstrated positive staining of IgM, C4, and C1q. Electron microscopy exhibited mesangial expansion with inflammatory cells and a lobular structure, suggesting membranoproliferative glomerulonephritis. Subendothelial deposits containing microtubular structures with a diameter of approximately 30–200 nm were found, concurrent with the criteria for the diagnosis of ITG. Screening for lymphoproliferative diseases and immunological abnormalities revealed a positive direct Coombs test result and the presence of cold agglutinins. Paraproteinemia was absent. The similarities between cold agglutinin disease and ITG, including the production of autoantibodies and involvement of complement pathways, raise the possibility that cold agglutinins played a role in the development of ITG; however, we were unable to prove it due to difficulties in detecting cold agglutinins on renal histology. We discuss the possible implications for pathogenesis considering prior reports on nephrotic syndrome being potentially associated with cold agglutinins.

Keywords Immunotactoid glomerulonephritis · Cold agglutinin · IgM · Complement · Nephrotic syndrome

Introduction

Immunotactoid glomerulonephritis (ITG) is found on approximately 0.06% of native kidney biopsies [1]. ITG is characterized by the presence of immunoglobulin deposition on glomeruli and microtubular structures on electron microscopy [2]. Immunofluorescent studies often show positive staining for the expression of IgG and C3 [3]. ITG was associated with lymphoproliferative diseases in approximately 30–40% of cases in previous studies [1, 4]. The presence of monoclonal immunoglobulins may be involved in the pathogenesis of ITG [4]. Basic studies have suggested that defective clearance of immunoglobulins may lead to the formation of a tactoid or microtubule structure [5, 6]. However, the scarcity of these cases precludes an in-depth investigation into its pathogenesis [7].

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Cold agglutinin disease (CAD) is caused by abnormal cold agglutinins, autoantibodies that bind to antigens on erythrocytes at a cold temperature, recruit complements, and subsequently induce hemolysis [8]. Patients with CAD present with hemolytic anemia, acrocyanosis, and/or a Raynaud phenomenon when exposed to cold temperatures. Cold agglutinins in patients with CAD are usually monoclonal IgM, which frequently possesses a high thermal amplitude, defined as the highest temperature at which an antibody binds to its antigen [8]. In contrast, cold agglutinins in healthy individuals are polyclonal and have a lower thermal amplitude, usually 15–20 °C, preventing the occurrence of hemolysis at the normal body temperature [8]. The production of pathogenic cold agglutinins has been associated with lymphoproliferative diseases, mycoplasma infection, and other infections [8]. Nephrotic syndrome in patients with CAD has been reported previously; however, whether these two conditions are pathogenetically related has not been proven [9–11].

Here, we report a case of nephrotic syndrome in a Japanese man with cold agglutinins. Light microscopy and immunofluorescent studies demonstrated membranoproliferative glomerulonephritis (MPGN) with positive staining for the expression of IgM, C4, and C1q. Electron microscopic analyses revealed the presence of subendothelial glomerular deposits containing microtubular structures, leading to a final diagnosis of ITG. Although hypothetical, given the similarities between CAD and ITG, including the involvement of abnormal immunoglobulins and complement systems, we considered the possibility that cold agglutinins might be involved in the pathogenesis of ITG. We also conducted a literature review on nephropathy in patients with positive cold agglutinins to discuss possible implications for pathogenesis. The patient's consent was obtained for writing this case report.

Case report

An 86-year-old Japanese man with a history of hypertension, dyslipidemia, and gastric malignancy presented to our outpatient clinic for the evaluation of proteinuria and hematuria. He had been visiting a nearby urology clinic for benign prostatic hyperplasia (BPH). One month prior to referral to our department, his blood pressure increased to approximately 200 mmHg, and his urinalysis showed proteinuria and hematuria. His medications included antihypertensives (losartan potassium and amlodipine), atorvastatin calcium hydrate, mecobalamin, difenidol, mirtazapine, flunitrazepam, nitrazepam, acetaminophen, and eperisone hydrochloride. He had been taking an herbal extract mixture for treating BPH. His family history was remarkable for malignancy in his maternal side. His mother had a subarachnoid hemorrhage. He

was a former smoker with 80-pack years. He quit drinking alcohol at the age of 60. He had no known allergies. He reported no recent history of infections or a history of hematologic diseases. On admission, physical examination revealed mild bilateral edema of the lower extremities. Vital signs showed an elevated blood pressure of 200/77 mmHg. He weighed approximately 71 kg, which had been stable for the past several years. Initial blood test results revealed renal impairment (creatinine, 1.37 mg/dL; estimated glomerular filtration rate, eGFR 38.3 mL/min/1.73 m²) and hypoalbuminemia (albumin, 2.6 g/dL). His estimated daily urinary protein was 5.89 g/g creatinine, meeting the diagnostic criteria for nephrotic syndrome (Table 1). Microscopic hematuria was also noted. The serologic screening test result for glomerulonephritis revealed a positive rheumatoid factor. The selectivity index for proteinuria indicated a low selectivity for urinary protein (0.329). Complement levels were within normal range. Ultrasonography of the kidneys showed a slightly larger left kidney (left kidney 126.7 mm × 58.7 mm; right kidney 114.0 mm × 58.7 mm). Chest radiography showed a cardiothoracic ratio of 54.2% with no sign of pleural effusion.

Impaired renal function, nephrotic syndrome, and microscopic hematuria suggested the possibility of glomerulonephritis. To elucidate the cause of nephrotic syndrome and microscopic hematuria, we performed a biopsy of the right kidney.

Kidney biopsy findings

The renal biopsy specimen included a total of 16 glomeruli, two of which demonstrated global sclerosis and two of which showed focal sclerosis. A moderate degree of mesangial proliferation was observed without apparent sclerosis (Fig. 1a, b). The level of interstitial fibrosis was approximately 30% (Fig. 1d). Immunofluorescence studies demonstrated coarse granular deposits of IgM, C4, C1q, and C3c along the glomerular capillary wall, and no apparent depositions of IgG and IgA (Fig. 2a). IgM deposits were present in the mesangial areas. Kappa staining was positive, while lambda staining was slightly positive (Fig. 2b). Electron microscopy exhibited mesangial expansion with inflammatory cells and a lobular structure, suggesting a membranoproliferative glomerulonephritis (MPGN) pattern. Subendothelial deposits were present, containing microtubule structures with a diameter of approximately 30–200 nm (Fig. 3a–c). Deposits were also found in the mesangial areas. DnaJ homolog subfamily B member 9 (DNAJB9) staining was negative (Fig. 2b), making fibrillary glomerulonephritis (GN) less likely. Direct fast scarlet 4BS (DFS) and Congo-red staining of the glomeruli were negative (Fig. 1c), suggesting that amyloidosis was unlikely [12]. Cryofibrinogen-associated glomerulonephritis was also on the list of differential diagnoses, because

Table 1 Laboratory findings on admission

<i>Blood counts</i>	
White blood cell	5900/ μ L
Red blood cell	418×10^4 / μ L
Hemoglobin	12.3 g/dL
Platelet	24.5×10^4 / μ L
Reticulocyte	10‰
<i>Blood chemistry</i>	
Sodium	147 mEq/L
Potassium	4.1 mEq/L
Chloride	112 mEq/L
Calcium	8.3 mg/dL
Phosphorus	2.8 mg/dL
Magnesium	2.2 mg/dL
Urea nitrogen	20 mg/dL
Creatinine	1.37 mg/dL
Total protein	5.8 g/dL
Albumin	2.6 g/dL
LDH	237 U/L
AST	22 U/L
ALT	13 U/L
ALP	201 U/L
γ GTP	27 U/L
CK	40 U/L
C reactive protein	0.41 mg/dL
HDL cholesterol	46 mg/dL
LDL cholesterol	95 mg/dL
Blood glucose	90 mg/dL
HbA1c	5.6%
IgG	1249.9 mg/dL
IgA	314.5 mg/dL
IgM	101.8 mg/dL
Rheumatoid factor	27.7 U/mL
Anti-nuclear antibody	40
CH50	43.5/mL
PR3-ANCA	< 1.0 U/mL
MPO-ANCA	< 1.0 U/mL
Anti-GBM antibody	< 2.0 U/mL
Anti-SM antibody	Negative
Anti-dsDNA antibody	Negative
Anti-CCP antibody	< 0.6 U/mL
Anti-Scl-70 antibody	Negative
Anti-SS-A/Ro antibody	Negative
Anti-SS-B/La antibody	Negative
Anti-centromere antibody	Negative
Serum electrophoresis	All negative
Urine electrophoresis	All negative
HBs antigen	Negative
HBs antibody	Positive
HBc antibody	Positive
HBV-DNA	Negative
HC antibody	Negative

Table 1 (continued)

TPLA	Negative
RPR	Negative
<i>Urine test</i>	
Urine protein	4+
Urine blood	1+
Urine white blood cell	negative
Specific gravity	1.027
Urine urobilinogen	$\pm$
Urine bilirubin	negative
Urinary protein–creatinine ratio	5.89 g/g creatinine
<i>Urine sediment</i>	
Red blood cells	5–9 per high power field
White blood cells	1–4 per high power field
Granular casts	20–29 per whole field
Waxy casts	5–9 per whole field
Fatty casts	10–19 per whole field

LDH lactate dehydrogenase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γ GTP* gamma-glutamyl transferase, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *HbA1c* hemoglobin A1c, *GBM* glomerular basement membrane, *dsDNA* double-strand DNA, *CCP* cyclic citrullinated peptide, *Scl* scleroderma, *SS-A* Sjögren's-syndrome-related antigen A, *HB* hepatitis B, *HC* hepatitis C, *TPLA* *Treponema pallidum* latex agglutination, *RPR* rapid plasma regain

the observed electron-dense deposits were similar to those of previously published case reports [13, 14]; however, the presence of immunoglobulin deposition on immunofluorescence microscopy argued against its possibility. These pathological findings suggested immunotactoid glomerulonephritis (ITG) as the most likely diagnosis.

Laser microdissection and mass spectrometry studies

To evaluate the composition of the microtubular structure, we conducted laser microdissection and mass spectrometry studies of the glomeruli; these revealed the presence of immunoglobulins and complements (Table 2). These findings were consistent with those in previous reports on ITG [4, 14].

Evaluation of comorbid conditions

Because a significant proportion of patients with ITG was previously found to have lymphoproliferative diseases, we performed serological screening tests. The M-peak was absent on serum and urine electrophoresis. We also performed a computed tomography (CT) of the chest and abdomen; it did not reveal apparent lymphadenopathy. However, CT showed enlargement of the prostate, and blood test revealed elevated total prostate surface antigen

Fig. 1 **a** Periodic acid Schiff staining of kidney sections from the patient. **b** Periodic acid–methenamine–silver staining of kidney sections from the patient. **c** Direct fast scarlet 4BS staining of kidney

sections from the patient was negative. **d** Masson's trichrome staining of kidney sections from the patient. The level of interstitial fibrosis was approximately 30%

level (27.3 ng/mL), prompting us to consult urologists in our hospital. Prostate biopsy histology revealed the presence of prostate cancer. Thereafter, the patient was started on hormone therapy.

We also evaluated the presence of cryoproteins, including cryoglobulin and cold agglutinins, because cryofibrinogen-associated glomerulonephritis was also suspected based on the presence of unusual electron-dense deposits on electron microscopy. Interestingly, the cold-agglutinin titer was elevated, while cryoglobulin was absent. Direct Coombs tests were positive for anti-IgG and negative for anti-C3d antibodies. Mycoplasma antibody was absent. However, the patient did not meet the diagnostic criteria for CAD owing to the absence of cold-induced symptoms and hemolytic anemia.

In the meantime, the amount of proteinuria fluctuated, ranging from 0.5 to 3.0 g/g creatinine. The level of cold agglutinins also changed from 128-fold to 512-fold; however, the changes showed no relationship with the change in urinary protein levels or the change of seasons. Given the absence of apparent symptoms associated with CAD and nephrotic syndrome as well as poor remission rates and

concern for side effects of immunosuppressive therapy, we decided to continue supportive therapy with antihypertensives and diuretics.

Diagnosis:

Immunotactoid glomerulonephritis.

Discussion

Glomerular diseases with organized deposits are relatively rare causes of nephrotic syndrome [15]. These glomerulopathies include amyloidosis, fibrillary GN, and ITG. Among these, fibrillary GN and ITG present with negative Congo-red staining results on immunofluorescence studies [15]. Fibrillary GN exhibits randomly arranged fibrils with a diameter of 10–30 nm [16], while ITG presents with microtubules aligned in parallel with a diameter > 30 nm [2]. Proteomics studies have demonstrated the presence of complements (C3, C4, and C9) in fibrillary GN and ITG [15]. The histological and molecular findings in the present case

Fig. 2 Immunofluorescence findings. **a** Staining by IgG, IgA, IgM, C3, C4, and C1q (from top left to right bottom) showed coarse granular deposits of IgM, C4, C1q, and C3c along the glomerular capillary

wall and no apparent depositions of IgG and IgA. **b** DnaJ homolog subfamily B member 9 staining was negative. Kappa staining was positive, while lambda staining was slightly positive

suggested ITG as the most probable diagnosis. While paraproteinemia was absent, serological test results suggested abnormalities in the immunological profile, including positive cold agglutinins and positive direct Coombs test. The presence of cold agglutinins, which are usually IgM, and positive IgM staining on immunofluorescence microscopy raised the possibility that cold agglutinins played a role in the pathogenesis of ITG in this case.

While no previous studies have demonstrated an association between ITG and cold agglutinins, nephrotic syndrome in patients with cold agglutinins has been found in the literature [9–11, 17–21] (Table 3). In one case, a 66-year-old woman presented with CAD and nephrotic syndrome [9]. Light microscopy showed normal-appearing glomeruli. The authors speculated that cold agglutinin and the complement system might be involved in the damage to the glomerular basement membrane and proteinuria [9]. A 51-year-old

Japanese man who developed pruritis in the spring and lower extremity edema in the winter was diagnosed with hemolytic anemia and nephrotic syndrome [19]. His cold agglutinins were significantly elevated by 2048-fold. The renal biopsy specimen demonstrated membranous nephropathy, and immunofluorescence microscopy showed coarse granular deposits of IgG, IgA, and C3 along the glomerular basement membrane and granular positivity for IgM in the mesangial region. Electron microscopy indicated the presence of electron-dense deposits in the subepithelial, sub-endothelial, and mesangial regions [19]. In a more recent case, a 96-year-old man developed acrocyanosis and pain on the face, auricle, and extremities in the autumn season and, subsequently, developed nephrotic syndrome in the winter [10]. Laboratory examinations revealed an abnormal IgM monoclonal band on serum electrophoresis and cold agglutinins, leading to the diagnosis of primary CAD. The authors

Fig. 3 Electron microscopy of kidney sections from the patient showing subendothelial deposits, containing microtubule structures with a diameter of approximately 30–200 nm. **a** Original magnification, $\times 5000$. **B** Original magnification, $\times 10,000$. **c** Original magnification, $\times 26,000$

Table 2 Mass spectrometry-based proteomic analysis

Identified proteins	UNIPROT ID	Molecular weight
<i>Immunoglobulins</i>		
Immunoglobulin kappa constant	[IGKC_HUMAN]	12 kDa
Ig gamma-1 chain C region	[IGHG1_HUMAN]	36 kDa
Ig lambda-2 chain C regions	[LAC2_HUMAN]	11 kDa
Immunoglobulin kappa variable 3–15	[KV315_HUMAN]	13 kDa
<i>Complement-related</i>		
Complement C3	[CO3_HUMAN]	187 kDa
Complement C4-A	[CO4A_HUMAN]	193 kDa
C4b-binding protein alpha chain	[C4BPA_HUMAN]	67 kDa
Complement component C9	[CO9_HUMAN]	63 kDa

suggested that his nephrotic syndrome might be related to CAD, although renal biopsy was not conducted [10]. These studies suggest the potential involvement of cold agglutinins, which are usually monoclonal IgM kappa, in the development of nephrotic syndrome.

Although these prior reports as well as our case suggest the possibility that cold agglutinins were associated with the onset of nephrotic syndrome, we were unable to prove the involvement of cold agglutinins, largely due to the inability

to detect cold agglutinins on renal histology. Moreover, our case did not meet the diagnostic criteria for CAD, as with some previous reports [11, 21], questioning the pathogenicity of cold agglutinins. To evaluate the potential involvement of cold agglutinins in glomerulopathy, future studies should address the following questions: (1) Are red blood cell antigens targeted by cold agglutinins, such as I antigens, expressed on renal cells? (2) Is the presence of monoclonal immunoglobulins or CAD necessary for cold agglutinins to

Table 3 Prior studies on nephrotic syndrome in patients with positive cold agglutinins

Author	Year	Patient characteristics						
		Age	Gender	Cold-associated symptoms	Hemolytic anemia	Nephrotic syndrome	Renal biopsy	Renal biopsy (immunofluorescence)
Poth [9]	1970	66	F	Thrombophlebitis, Raynaud's phenomenon	Yes	Yes	Normal ^a	Not available
Bailey [17]	1972	24	M	Arthralgia, severe muscle cramps	Yes	Yes	Tuft obliterated by eosinophilic material	Focal glomerular deposits of IgM and beta immune complex, granular aggregates of IgG and IgA
Skarin [18]	1978	56	F	Joint pains and stiffness, rash, Raynaud's phenomenon	No	Partially ^b	Not available	Not available
Hirano [19]	1983	51	M	Prurigo	Yes	Yes	MN	IgG,IgA,C3 coarse granular on GBM, IgM granular in mesangium
Shibasaki [11]	1991	31	M	None	No	Yes	MPGN	Not available
Gupta [20]	2011	62	M	Jaundice, splenomegaly	Yes	Partially ^b	Nodular glomerulosclerosis	No deposition
Basford [21]	2011	59	M	Not mentioned	No	Partially ^b	MN with crescents	IgG
Hamasaki [10]	2014	96	M	Acrocyanosis, limb pain	Maybe	Yes	Not available	Not available

^aImmunofluorescent and electron microscopic studies could not be performed

^bPartially means that patients met one of the diagnostic criteria of nephrotic syndrome: low serum total protein/albumin level or proteinuria

MN membranous nephropathy, MPGN membranoproliferative glomerulonephritis

deposit in the glomeruli? (3) Can we develop methods to detect cryoproteins on renal histology?

The optimal treatment strategy for ITG has not been firmly established [4]. As for the secondary form, therapies against the underlying conditions may be effective [22]. Some reports demonstrated the potential utility of immunosuppressive therapy [4], while others indicated low remission rates (fewer than 10%) [6]. It is particularly important for clinicians to weigh the risks and benefits of treatment, especially in elderly patients, who may be at an increased risk of side effects due to immunosuppression, such as infections and diabetes [23]. In the present case, we considered that the harm of immunosuppressive treatments would outweigh their benefits, given the absence of cold-induced symptoms, decline in proteinuria with supportive therapy, and his old age.

We encountered a rare case of ITG in a patient with cold agglutinins. Nephrotic-range proteinuria and edema subsided with the use of antihypertensive and diuretic therapy, prompting us not to initiate immunosuppressive therapy. Given the previous reports on nephrotic syndrome's potential association with cold agglutinins, we considered the

possibility that cold agglutinins might be involved in our patient's glomerulopathy; however, we were not able to prove the association. Further studies on the relationship between cold agglutinins and ITG are warranted to elucidate the mechanism of pathogenesis and develop optimal management strategies.

Declarations

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

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