IgA nephropathy in a boy with frequently relapsing nephrotic syndrome

Ichikawa, Yuta ; Horinouchi, Tomoko ; Tanaka, Yu ; Ueda, Chika ; Kitakado, Hideaki ; Kondo, Atsushi ; Sakakibara, Nana ; Yoshikawa,…

(Citation)
CEN Case Reports,13(1):14-18

(Issue Date)
2024-02

(Resource Type)
journal article

(Version)
Accepted Manuscript

Title Page

Title

IgA nephropathy in a boy with frequently relapsing nephrotic syndrome

Yuta Ichikawa[1], Tomoko Horinouchi[1], Yu Tanaka[1], Chika Ueda[1], Hideaki Kitakado[1], Atsushi Kondo[1], Nana Sakakibara[1], Norishige Yoshikawa[2], Kandai Nozu[1]

[1] Department of Pediatrics, Kobe University Graduate School of Medicine, Kusunokicho 7-5-1, Chuo-ku, Kobe, Hyogo, Japan.

[2] Clinical Research Center, Takatsuki General Hospital, 1-3-13 Kosobe-cho, Takatsuki, Osaka, Japan

Corresponding author

Tomoko Horinouchi MD, PhD

Department of Pediatrics, Graduate School of Medicine, Kobe University,

7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Tel: +81-382-6090; Fax: +81-382-6099; E-mail: tohori@med.kobe-u.ac.jp

The number of words in the manuscript: 1412

Abstract

A Japanese boy developed nephrotic syndrome (NS) and had microscopic hematuria at 8 years old. Renal biopsy was performed. Light microscopy study revealed mesangial proliferation and all immunofluorescent stains (including IgA) were negative, so he was diagnosed with non-IgA diffuse mesangial proliferation (DMP). Complete remission was achieved at 13 days after the initiation of oral prednisolone, and hematuria also disappeared three days later, but the patient developed frequently relapsing nephrotic syndrome (FRNS). Cyclosporine A (CyA) was introduced at 10 years old, and there were no relapses between then and when it was discontinued at 12 years old. A second renal biopsy revealed minimal change without CyA nephrotoxicity. However, there was repeated relapse of NS after discontinuation, so CyA was reintroduced eight months later, and NS remained in remission thereafter. Microscopic hematuria appeared at 13 years old, however, with gross hematuria appearing at the time of infection. A third renal biopsy revealed mesangial proliferation with IgA-dominant deposition, so the patient was diagnosed with IgA nephropathy. Currently (14 years old), CyA treatment has been discontinued and the patient is undergoing lisinopril therapy for IgA nephropathy, but there are still relapses of NS. To the best of our knowledge, there have been no previous reports of a patient with non-IgA DMP at the onset of NS who had

later development of IgA nephropathy. The patient showed non-IgA DMP at the onset, suggesting that NS with non-IgA DMP and IgA nephropathy have some common pathophysiology. Treatment for NS, such as PSL and/or CyA treatment, may suppress the clinical manifestation of late IgA nephropathy.

Keywords

nephrotic syndrome (NS), non-IgA diffuse mesangial proliferation (DMP), frequently relapsing nephrotic syndrome (FRNS), cyclosporine A (CyA), IgA nephropathy

Introduction

The most common form of childhood nephrotic syndrome (NS) is idiopathic NS (INS), and many of its pathological findings are minimal change disease (MCD) [1]. More than 90% of cases of MCD respond well to prednisolone (PSL) therapy, so treatment of childhood INS typically begins with an initial trial of PSL therapy [2]. Persistent hematuria suggests other pathological findings besides MCD, however, and is an indication for the necessity of the renal biopsy before treatment [3, 4]. Among cases of childhood INS with hematuria, those with mesangial proliferation without IgA deposition by immunofluorescence are classified, for example, as diffuse mesangial hypercellularity (DMH) or non-IgA diffuse mesangial proliferation (DMP) [4-9]. The clinical features of DMH/non-IgA DMP require more detailed clarification.

By contrast, IgA nephropathy is the most common form of chronic glomerulonephritis in Japan. The prognosis has recently been improved by early and appropriate therapeutic intervention; renal survival probability is 98.8% at 15 years for children with IgA nephropathy [10]. IgA nephropathy in some cases meets the diagnostic criteria for NS, but the incidence is low and the course differs from that of typical INS [11, 12].

We report the case of a Japanese boy that developed IgA nephropathy during the course of treatment for frequently relapsing NS (FRNS). At the onset of NS, pathological

findings showed non-IgA DMP.

Case report

The patient developed NS at eight years of age. He had no remarkable medical history and no family history of kidney disease or hearing loss. Also, annual school urine screening tests had never detected proteinuria or hematuria. He presented with edema, hypoalbuminemia (serum albumin: 1.3 mg/dl), severe proteinuria (urine protein creatinine ratio: 15.1 g/gCr) and 'typical' childhood INS, with the exception of microscopic hematuria (urine-red blood cells: 30-49/high power field) (Table 1). Persistent hematuria suggested something other than minimal change disease, so an initial renal biopsy was conducted before starting treatment. Light microscopy study revealed diffuse mesangial proliferation. All immunofluorescent stains, including IgA, were negative (Fig.1a). Electron microscopy study also revealed mesangial proliferation and foot process effacement, but there were no dense deposits (Fig.1d); diagnosis was non-IgA DMP. Complete remission was achieved 13 days after the initiation of oral PSL (60 mg/m^2/day), and hematuria also disappeared by the 16^{th} day. The course was thought to be consistent with DMP. PSL was administered at a dose of 60 mg/m^2 for a total of four weeks and then 40 mg/m^2 for four weeks, in accordance with published guidelines [13].

Although he had steroid-sensitive NS, he relapsed 9, 11, 15, and 16 months later, and was diagnosed with FRNS. CyA was therefore introduced at the age of 10 years and there was no relapse between then and discontinuation two years later (12 years old). At that time, a second renal biopsy was taken (Table 1, Fig.2) and light microscopy study revealed no CyA nephrotoxicity with minimal change (Fig.1b). Immunofluorescent staining and electron microscopy study were not performed. The patient did not develop steroid-resistant NS. Although he had steroid-sensitive NS, he had relapse at 1, 4, 5, and 8 months later, and CyA was reintroduced. During the second course of CyA treatment, there were no further relapses of NS, but microscopic hematuria appeared at 13 years old, and gross hematuria also sometimes appeared if he had an infection. A third renal biopsy was taken at 14 years old (Table 1, Fig.2). Light microscopy study revealed diffuse mesangial proliferation (Oxford classification: M1, E1, S0, T0, C0). IgA was positive in just the glomerular mesangial region, indicating IgA nephropathy (Fig.1c, 1f). Electron microscopy revealed no foot process effacement, but there were electron-dense deposits in the mesangium (Fig.1e). Galactose-deficient IgA1 (Gd-IgA1) was also positive in the glomerular mesangial region, which supports the diagnosis of IgA nephropathy (Fig. 1g-i) [14, 15]. Now 14 years old, the patient has discontinued CyA treatment and is receiving lisinopril therapy for focal IgA nephropathy, but he continues to have relapses of NS.

Discussion

Our patient was diagnosed with non-IgA DMP because of mesangial proliferation without IgA deposition, and because his urinary protein and microscopic hematuria quickly disappeared after beginning steroid therapy. He later had frequent relapses, microscopic and then eventually macroscopic hematuria. Aside from this re-emergence of microscopic hematuria and then emergence of macroscopic hematuria, the patient's clinical course was consistent with that of INS. However, he developed IgA nephropathy, evidenced both by pathological findings (mesangial proliferation with IgA-dominant deposition [Gd-IgA1 positivity]), and clinical findings (persistent microscopic hematuria and gross hematuria at the time of infections). The possibility that he had an coincidental combination of the two different diseases cannot be ruled out, but it should be noted that he had DMP (but IgA negativity) at the initial renal biopsy. This suggests that NS with non-IgA DMP could have common pathophysiology with IgA nephropathy.

To the best of our knowledge, there have been no previous reports of a patient with non-IgA DMP at the onset of NS who had later development of IgA nephropathy. The course of this case is thus thought to be very unusual. However, Maekawa et al. [15] reported a similar case in which a girl with NS had FRNS at 3 years old. Microscopic hematuria

appeared at 17 years old, and a renal biopsy at 19 years old showed mesangial proliferation with IgA-dominant deposition. She was diagnosed with IgA nephropathy, although the renal pathology at the onset of NS was unknown. Elsewhere, Umeda et al. [16] reported the case of a girl with IgA nephropathy that was diagnosed with NS at 5 years old. She had IgA deposition and minimal change at the initial renal biopsy. Microscopic hematuria and gross hematuria developed at 9 years old, and after 16 incidences of relapse, renal biopsy showed mesangial proliferation with IgA-dominant deposition. Taken together with our patient's case, we suggest the possibility of latent IgA nephropathy in childhood INS, which has the potential to become symptomatic. Frequent relapses of NS may also contribute to the development of IgA nephropathy in some cases. Treatment for NS, such as PSL and CyA treatment, may suppress the clinical manifestation of late IgA nephropathy. Although there are few such reported cases and the conclusions are speculative, it is hoped that this case will trigger further investigations.

Acknowledgements We acknowledge proofreading and editing by Benjamin Phillis.

Declarations

Conflict of interest: The authors declare that no conflict of interest exists.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number B190137) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by the authors.

Informed consent: The patient's parents provided a signed informed consent form for publication of the case report.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018; 392:61-74.
2. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. J Pediatr. 1981; 98:561-4.
3. Childhood nephrotic syndrome associated with diffuse mesangial hypercellularity. A report of the Southwest Pediatric Nephrology Study Group. Kidney Int. 1983; 24:87-94.
4. Hama T, Nakanishi K, Shima Y, Sato M, Mukaiyama H, Togawa H et al. Renal biopsy criterion in idiopathic nephrotic syndrome with microscopic hematuria at onset. Pediatr Nephrol. 2015; 30:445-50.
5. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int. 1978; 13:159-65.
6. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. Kidney Int. 1981; 20:765-71.
7. Border WA. Distinguishing minimal-change disease from mesangial disorders. Kidney Int. 1988; 34:419-34.
8. Jennette JC, Hipp CG. Immunohistopathologic evaluation of C1q in 800 renal biopsy specimens. Am J Clin Pathol. 1985; 83:415-20.
9. Orfila C, Pieraggi MT, Suc JM. Mesangial isolated C3 deposition in patients with recurrent or persistent hematuria. Lab Invest. 1980; 43:1-8.
10. Yata N, Nakanishi K, Shima Y, Togawa H, Obana M, Sako M et al. Improved renal survival in Japanese children with IgA nephropathy. Pediatr Nephrol. 2008; 23:905-12.
11. Kim JK, Kim JH, Lee SC, Kang EW, Chang TI, Moon SJ et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol. 2012; 7:427-36.
12. Shima Y, Nakanishi K, Sato M, Hama T, Mukaiyama H, Togawa H et al. IgA nephropathy with presentation of nephrotic syndrome at onset in children. Pediatr Nephrol. 2017; 32:457-65.
13. Ishikura K, Matsumoto S, Sako M, Tsuruga K, Nakanishi K, Kamei K et al.

Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: medical therapy. Clin Exp Nephrol. 2015; 19:6-33.

14. Suzuki H, Yasutake J, Makita Y, Tanbo Y, Yamasaki K, Sofue T et al. IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis. Kidney Int. 2018; 93:700-5.
15. Ishiko S, Horinouchi T, Fujimaru R, Shima Y, Kaito H, Tanaka R et al. Glomerular galactose-deficient IgA1 expression analysis in pediatric patients with glomerular diseases. Sci Rep. 2020; 10:14026.
16. Maekawa K, et al. A case of overlap syndrome with frequent relapsing nephrotic syndrome accompanied by IgA nephropathy. Japanese Journal of Pediatric Nephrology. 2014; 27(suppl): 210. (in Japanese)
17. Umeda C, et al. A 9-year-old girl developed IgA nephropathy after rituximab treatment for steroid-dependent minimal change nephrotic syndrome. Journal of Japanese Society for Pediatric Renal Failure. 2019; 39: 111-14.

Figure Legends.

Fig.1: Light microscopy study at 8 years old showed diffuse mesangial proliferation. No deposition was shown in immunofluorescent study including IgA (1a, periodic acid-Schiff stain, original magnification × 400). Electron microscopy study at the same time showed mesangial proliferation and foot process effacement, but there were no dense deposits (Fig.1d). Light microscopy study at 12 years old showed minimal change in the disease without CyA nephrotoxicity. Immunofluorescent study was unavailable at that time (1b, periodic acid-Schiff stain, original magnification × 400). Light microscopy at 14 years old showed diffuse mesangial proliferation, and IgA deposition was shown in the immunofluorescent study, which indicate IgA nephropathy (1c, periodic acid-Schiff stain, original magnification × 400; 1f, green, IgA). Electron microscopy study at that time showed no foot process effacement, but there were dense deposits in the mesangium (1e). Immunofluorescent study at 14 years old showed that IgA (1g, red) and Gd-IgA (1h, green) were both positive (1i, merged).

Fig.2. Clinical course

At the onset of NS (8 years old), the patient underwent an initial renal biopsy. He relapsed four times within a year, and was diagnosed with FRNS, so CyA was introduced at 10 years old. There were no relapses after the initiation of CyA, and the administration of CyA was discontinued after two years (12 years old). At the same time, a second renal

biopsy was conducted. After that, he relapsed four times within a year, and CyA was reintroduced eight months later. During the second course of CyA treatment, he had no relapses of NS, but microscopic hematuria appeared at 13 years old. He underwent a third renal biopsy at 14 years old. (NS: nephrotic syndrome)

Table 1: Laboratory data at the time of admission for the first, second and third renal biopsies.

	First renal biopsy	Second renal biopsy	Third renal biopsy	
【Blood test】				
WBC	8300	5500	4800	/μl
Hb	12.2	10.6	12.2	g/dl
Plt	35.4×10^4	28.6×10^4	30×10^4	/μl
CRP	0.03	0.02	0.02	mg/dl
BUN	22.6	13	20.8	mg/dl
Cre	0.47	0.41	0.71	mg/dl
eGFR	94.6	143	110	$ml/min/1.73m^2$
UA	5.5	4.1	8.2	mg/dl
TP	4.5	7.1	7.6	mg/dl
Alb	1.3	3.8	4.2	mg/dl
IgG	709	1573	1486	mg/dl
IgM	221	173	182	mg/dl
IgA	235	255	321	mg/dl
【Urinalysis】				
Pro	4+	+-	1+	
OB	3+	+-	3+	
Glu	-	-	-	
Upro/Ucr	15.1	0.14	0.12	

RBC	30-49	1-4	50-99	/HPF
β2MG	540	43	36	μg/L

WBC: white blood cell, Hb: hemoglobin, Plt: platelet, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, TP: total protein, Alb: albumin, IgG: immunoglobulin G, IgM: immunoglobulin M, IgA: immunoglobulin A, Pro: protein, OB: occult blood, Glu: glucose, Upro/Ucr: urinary protein creatinine ratio, RBC: red blood cell, HPF: high power field, β2MG: β2-microglobulin

Fig.1a

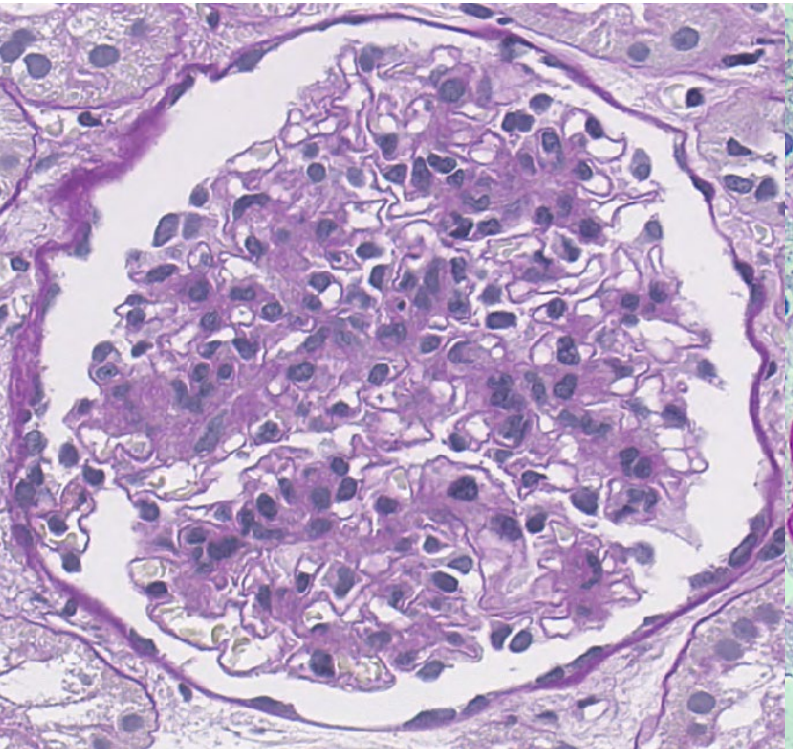


Fig.1b

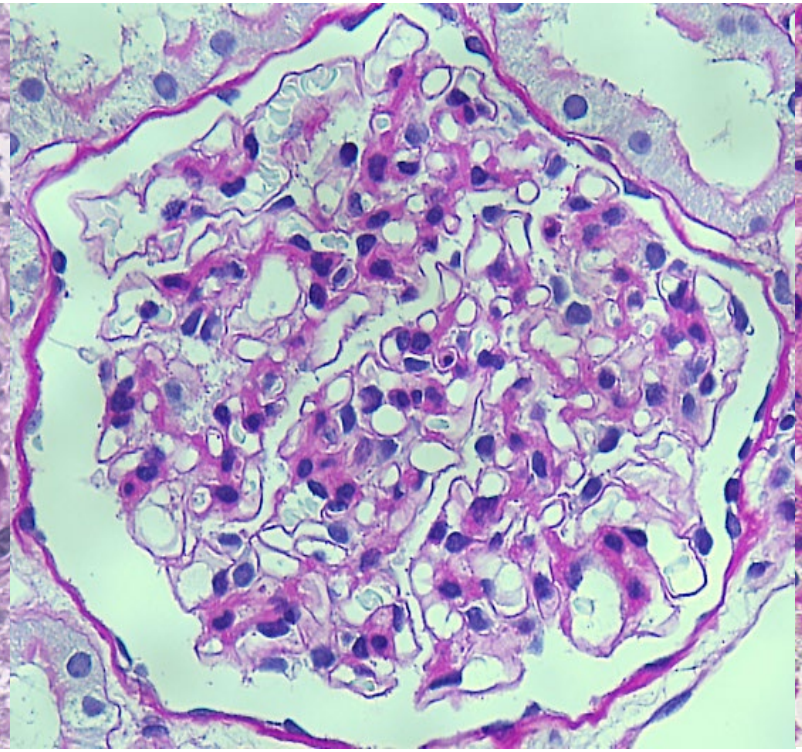


Fig.1c

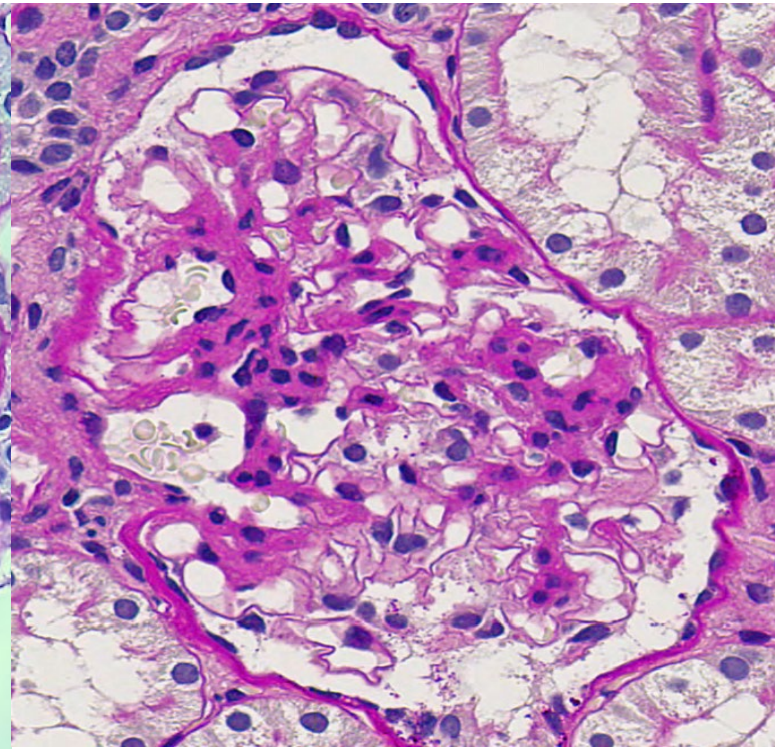


Fig.1d

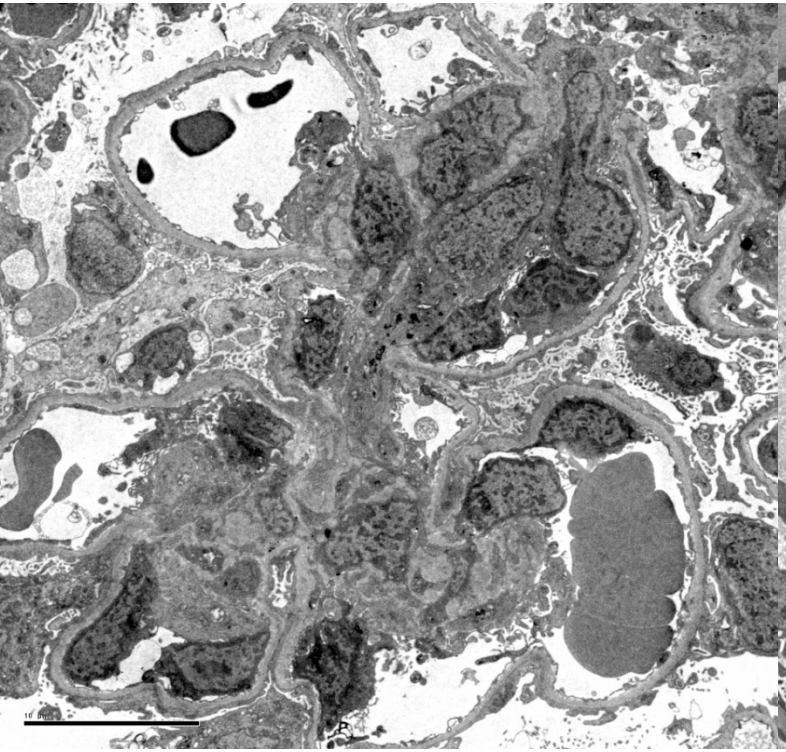


Fig.1e

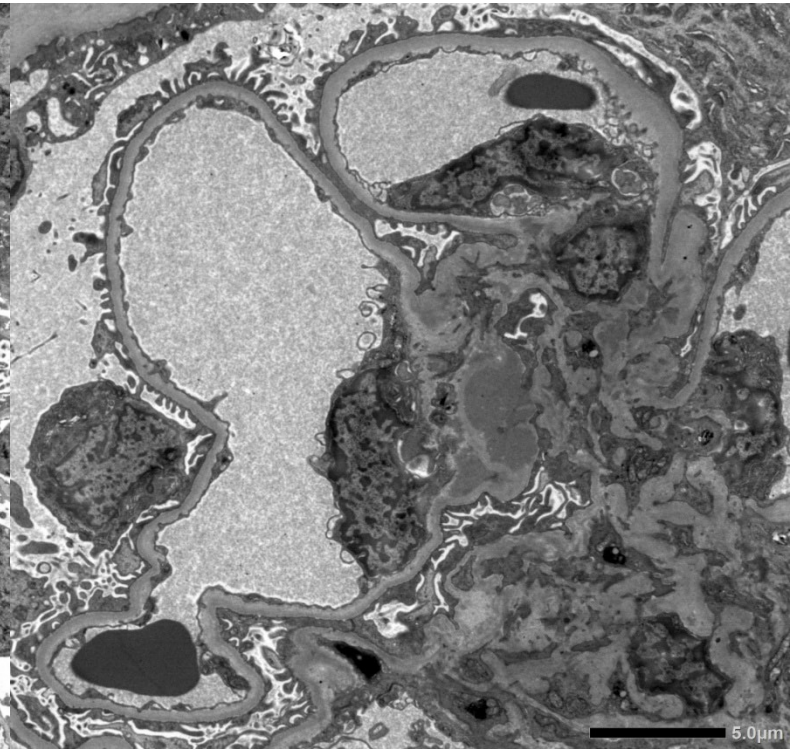


Fig.1f

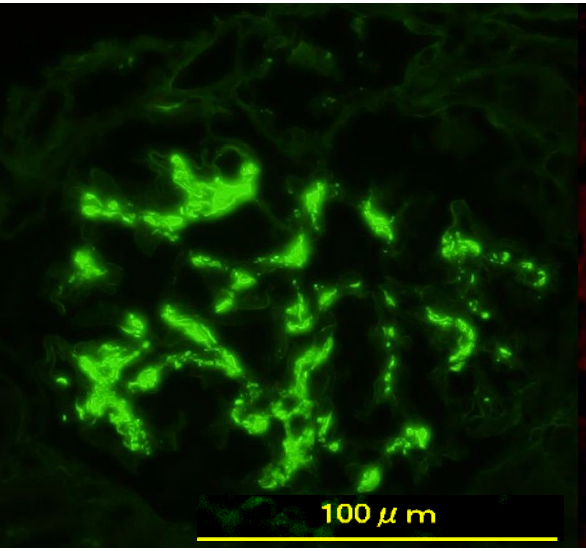


Fig.1g

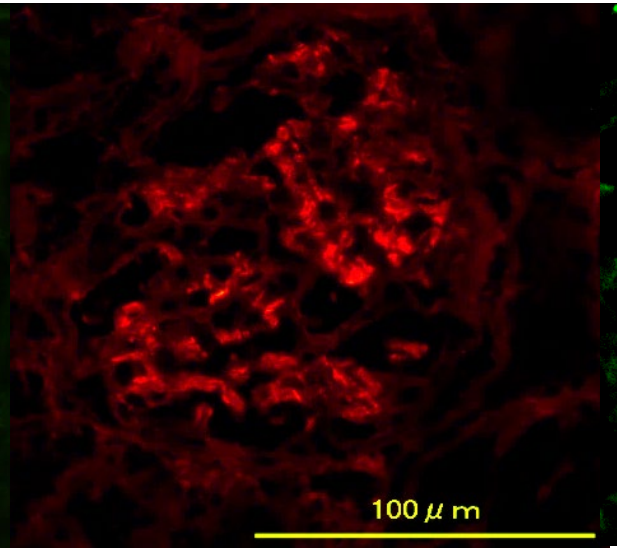


Fig.1h

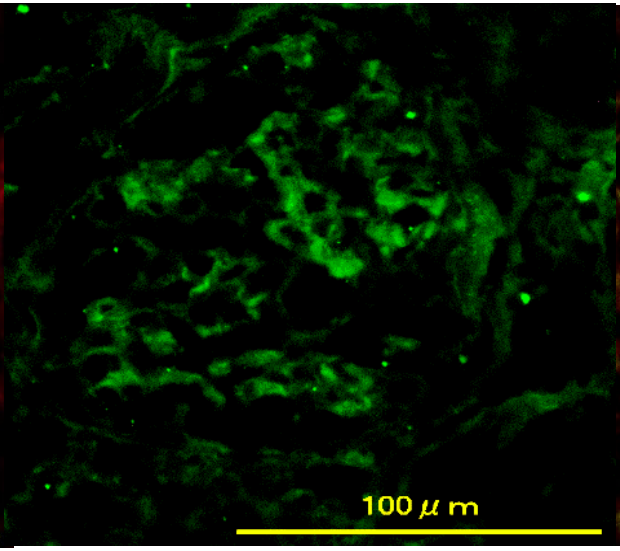


Fig.1i

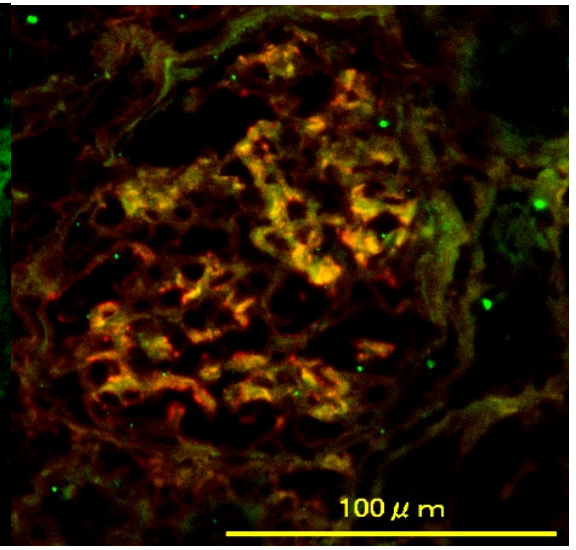
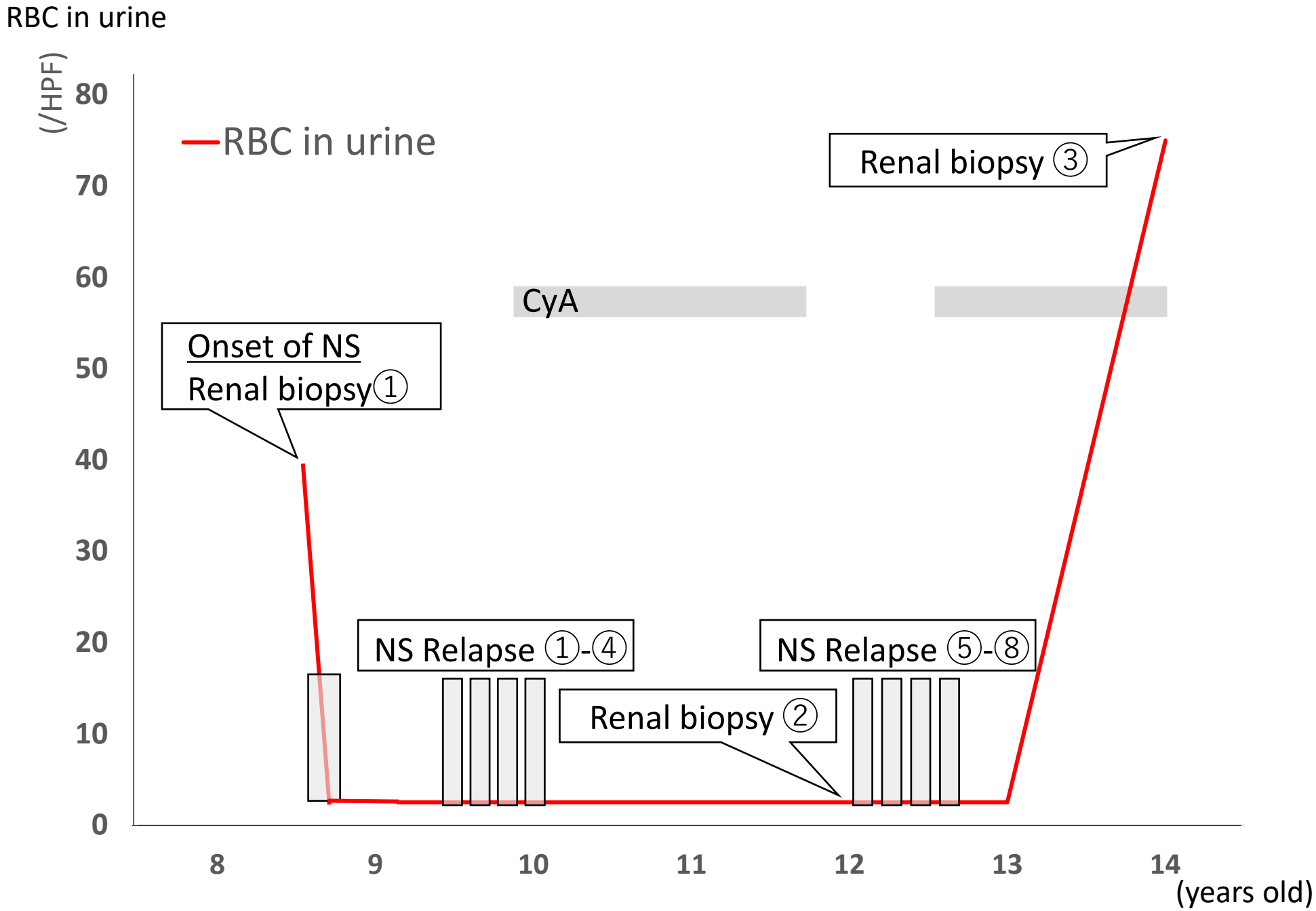


Fig.2


RBC in urine
(/HPF)
80
70
60
50
40
30
20
10
0
RBC in urine
Renal biopsy ③
CyA
Onset of NS
Renal biopsy①
NS Relapse ①-④
NS Relapse ⑤-⑧
Renal biopsy ②
8
9
10
11
12
13
14
(years old)