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Case Report

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Lupus anticoagulant-hypoprothrombinemia syndrome with lupus nephritis in a girl misdiagnosed with immunoglobulin A nephropathy: a case report

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Distinguishing lupus nephritis (LN) from other glomerulopathies, such as immunoglobulin A nephropathy (IgAN), poses a diagnostic challenge owing to overlapping clinical and histopathologic findings. Lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) is a rare and potentially fatal disorder characterized by the presence of lupus anticoagulant and acquired factor II deficiency. We report a pediatric case of LN with LAHPS, which was initially diagnosed as IgAN. An 8-year-old girl presented with gross hematuria with nephrotic syndrome. Based on the kidney biopsy results, treatment for IgAN with membranoproliferative pattern was initiated. Two months later, she developed left upper extremity swelling with multiple vein thromboses requiring anticoagulation; treatment led to remission, allowing discontinuation of immunosuppressants within 8 months. Gross hematuria recurred 10 months later and was accompanied by hypocomplementemia; positive antinuclear, anti-double stranded DNA, and triple antiphospholipid antibodies; and factor II deficiency, prompting revision of the diagnosis to LN and LAHPS. Initial delay in LN diagnosis was attributed to the patient's young age, nonspecific symptoms, and inconclusive laboratory and histopathological findings. Immunosuppressive therapy for IgAN partially improved LN, further complicating the diagnosis. This case emphasized the importance of clinical suspicion; integrating clinical, serological, and histopathological data; and considering LAHPS in differential diagnosis of glomerulonephritis with coagulopathy.

Keywords: Case reports; Glomerulonephritis, IGA; Hypoprothrombinemias; Lupus coagulation inhibitor; Lupus nephritis

Introduction

Lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS) is a rare disorder defined by the simultaneous presence of lupus anticoagulant (LA) and acquired factor II deficiency [1-4]. This condition increases the risk of both bleeding and thrombosis, which are potentially fatal. LAHPS is primarily associated with systemic lupus erythematosus (SLE) and infectious diseases and mostly affects women and patients aged ≤16 years [1-4]. LAHPS often occurs in the context of antiphospholipid syndrome (APS), which is an autoimmune condition characterized by the presence of antiphospholipid antibodies (aPL), including LA, anticardiolipin antibodies, and anti-β2 glycoprotein I (anti-β2GPI) antibodies [5]. SLE is a complex

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multisystem autoimmune disease that can affect various organ systems, with lupus nephritis (LN) being one of its most serious complications. The average age of pediatric SLE onset is 12 to 14 years, and onset before 10 years of age is rare [6]. Differentiating LN from other glomerular diseases, such as immunoglobulin A nephropathy (IgAN), is crucial because their clinical course, management, and prognosis differ significantly [7]. Notably, several kidney conditions, including Alport syndrome, can be misdiagnosed as IgAN, the most prevalent primary glomerular disorder, due to overlapping clinical and histological features. LN and IgAN may share findings such as mesangial proliferation, and a membranoproliferative glomerulonephritis (MPGN) pattern can further complicate their differentiation [7-9]. Here, we present a pediatric case of LN and LAHPS, which was initially misdiagnosed as IgAN with an MPGN pattern.

Case report

An 8-year-old girl presented to the emergency department of Seoul National University Children's Hospital with a 4-day history of fever and gross hematuria, accompanied by periorbital edema that developed on the day of the visit. She had a congenital single kidney and a history of epilepsy following encephalitis at the age of 2 years. Her family history included a maternal uncle who underwent kidney transplantation due to glomerulonephritis, and her mother and older sister experienced recurrent hematuria of unknown causes. However, there was no family history of autoimmune diseases, including SLE. Laboratory findings revealed profound proteinuria (urine protein-to-creatinine ratio [UPCR], 11.6 mg/mg) with hypoalbuminemia (2.7 g/dL), consistent with nephrotic syndrome, and red blood cell >100 per high power field in urinalysis, which suggested glomerulonephritis with mildly decreased kidney function (Table 1). The antinuclear antibody (ANA) was positive with a homogeneous pattern, along with marginally low to normal complement levels (C3/C4, 82/10 mg/dL), slightly elevated anti-double stranded DNA (anti-dsDNA) antibodies (21.3 IU/mL), and positive LA; the complete blood count was normal (Tables 1, 2). She had no clinical symptoms of SLE, such as rash, arthralgia, or alopecia. Kidney biopsy revealed IgAN (Oxford classification M1 S0 E1 T0) with an MPGN pattern, which was characterized by diffuse moderate hypercellularity of mesangial and endothelial cells, tram-track appearance, and moderate mesangial and subendothelial deposits with predominant IgA (3+) (Fig. 1). Oral glucocorticoid (GC) therapy with deflazacort 60 mg/m^2/day was initiated for 1 month; however, due to persistent nephrotic-range proteinuria with periorbital edema, mycophenolate mofetil (MMF) 400 mg/m^2/dose twice daily was added, with a gradual tapering of deflazacort. Two months after diagnosis, she presented to the emergency department because of left

Table 1. Laboratory findings of the patient

Variable	Upon IgAN diagnosis	Upon admission for thrombosis	Upon LAHPS diagnosis	Current (post-CPM treatment)	Reference range
WBC (/μL)	7,380	7,150	6,330	5,600	4,500–14,500
Hemoglobin (g/dL)	11.1	8.0	10.7	14.7	11.5–15.5
Platelet (×10^3/μL)	221	226	207	289	130–400
BUN/Cr (mg/dL)	19/0.48	32/0.94	40/1.4	10/0.51	-
Cystatin C (mg/L)	1.17	1.69	2.29	1.26	-
eGFR (mL/min/1.73 m^2)[a]	78.9	42.2	33.6	83.0	-
Albumin (g/dL)	2.7	2.7	3.6	1.8	3.3–5.2
Cholesterol (mg/dL)	409	546	178	Not done	0–240
Coagulation panel					
PT INR	0.89	0.90	1.56	1.16	0.8–1.2
aPTT (sec)	50.8	43.0	69.3	55.5	27.1–37.8
Fibrinogen (mg/dL)	325	415	286	425	192–411
Urine laboratory					
UPCR (mg/mg)	11.60	16.55	2.30	12.24	<0.2
RBC (/HPF)	≥100	≥100	≥100	10–19	0–4

IgAN, immunoglobulin A nephropathy; LAHPS, lupus anticoagulant-hypoprothrombinemia syndrome; CPM, cyclophosphamide; WBC, white blood cell; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; UPCR, urine protein-to-creatinine ratio (in the first-morning urine); RBC, red blood cell; HPF, high power field.
[a]Calculated by the Schwartz creatinine-cystatin C equation (2012).

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Table 2. Systemic lupus erythematosus-related laboratory profiles

Variable	Upon IgAN diagnosis	Upon admission for thrombosis	Upon LAHPS diagnosis	Current (post-CPM treatment)	Reference range
C3 (mg/dL)	82	105	45	125	70–150
C4 (mg/dL)	10	20	2	19	10–35
ANA	Positive (homogenous pattern)	Positive (1:40)	Positive (>1: 320)	ND	Negative
Anti-dsDNA Ab (IU/mL)	Positive (21.3)	Negative (<1.0)	Positive (907.5)	Negative (<1.0)	0–7
Anticardiolipin Ab, IgG (U/mL)	ND	Negative	Positive (71.7)	Negative	Negative
Anticardiolipin Ab, IgM (U/mL)	ND	Negative	Positive (24.2)	Positive (24.7)	Negative
Anti-β2GPI IgG (U/mL)	ND	Negative	Positive (344.0)	Positive (33.6)	Negative (<20)
Anti-β2GPI IgM (U/mL)	ND	Negative	Positive (32.0)	Positive (30.1)	Negative (<20)
LA	Positive	Positive	Positive	Positive	Negative

IgAN, IgA nephropathy; LAHPS, lupus anticoagulant-hypoprothrombinemia syndrome; CPM, cyclophosphamide; C3, complement component 3; C4, complement component 4; ANA, antinuclear antibody; ND, not done; dsNDA, double stranded DNA; Ab, antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; GPI, glycoprotein I; LA, lupus anticoagulant.

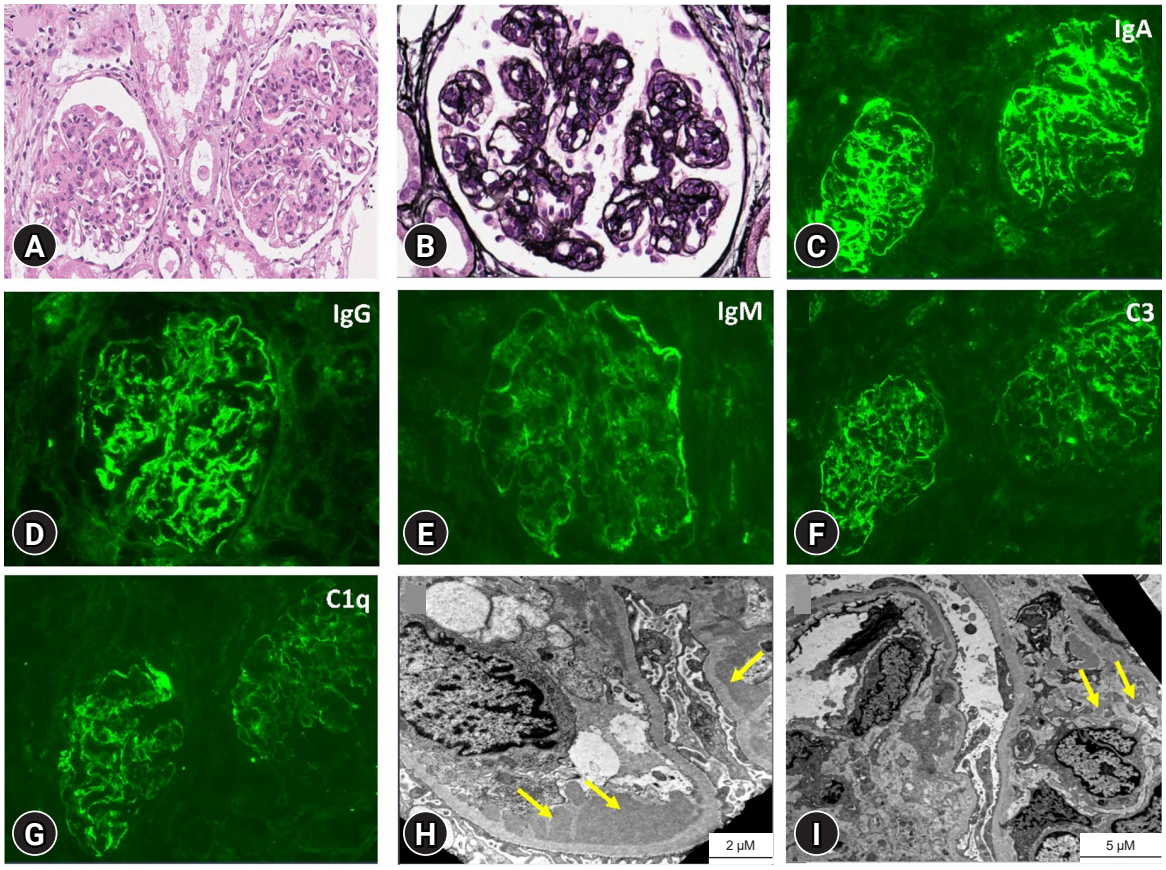

Fig. 1. Kidney biopsy findings. (A, B) Light microscopy shows diffuse moderate hypercellularity of mesangial and endothelial cells and increased mesangial matrix, which shows a tram-track pattern (A: hematoxylin and eosin stain, ×200; B: methenamine silver Periodic acid-Schiff stain, ×400). (C-G) Immunofluorescence staining shows IgA(3+), IgG(2+), IgM(1+), C3(2+), and C1q(2+) (C, F, G: ×200; D, E: ×400). Electron microscopy shows electron-dense deposits (+) with marked focal effacement of foot processes; moderate subendothelial (H) and mesangial (I) deposits (yellow arrows). The thickness of the glomerular basement membrane is within the normal limits (H, I).

upper extremity swelling. Imaging studies, including upper extremity Doppler ultrasound and computed tomography angiography, revealed multiple thromboses in the left axillary, subclavian, and brachial veins (Fig. 2). She was treated with

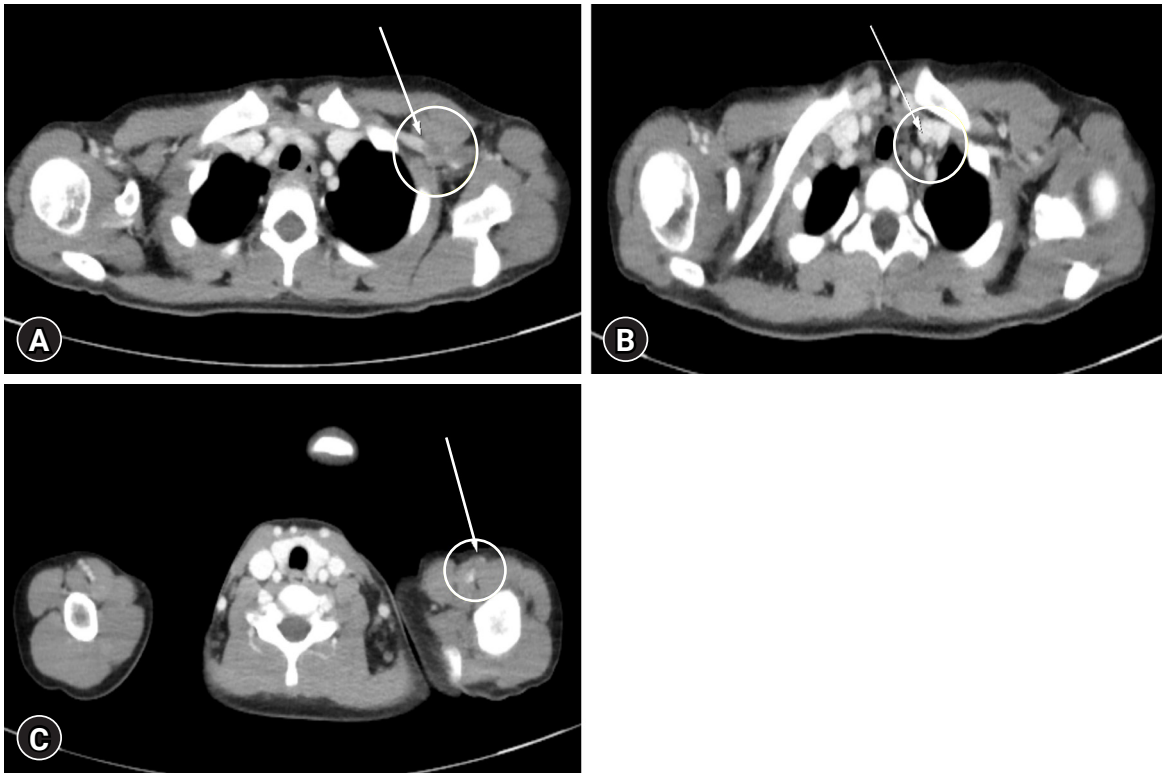

Fig. 2. Computed tomography angiography with three-dimensional upper extremity artery and vein (with contrast). There are multiple thromboses in the left axillary (A), subclavian (B), and brachial (C) veins (marked by a circle and an arrow).

intravenous heparinization followed by 4 months of oral warfarin, which resolved the thrombosis. The coagulation panel and tests for factors IX to XII to investigate the cause of the thrombosis were normal. At that time, SLE was suspected, and relevant tests were conducted. The results showed positive results for ANA and LA; however, complement levels, anti-dsDNA, anti-Smith, anti-cardiolipin, and anti-β2GPI antibodies were within normal ranges; therefore, she did not meet the diagnostic criteria for APS or SLE (Table 2). While on continued treatment with deflazacort (60 mg/m^2/day for 1 month, then tapered) and MMF (increased from 400 mg/m^2/dose to 600 mg/m^2/dose, twice daily), proteinuria achieved and maintained in remission, allowing for gradual tapering and eventual discontinuation of immunosuppressants (deflazacort at 6.5 months and MMF at 7 months). Thereafter, she was maintained on enalapril (0.1 mg/kg/day) alone. However, 10 months after stopping the immunosuppressants, she experienced gross hematuria recurrence, purpura on both legs, and recurrent epistaxis. Laboratory findings showed prolonged prothrombin time (PT) (international normalized ratio, 1.56) and activated partial thromboplastin time (aPTT) (69.3 seconds), hypocomplementemia (C3/C4, 45/2 mg/dL), acute kidney injury, and worsened proteinuria (UPCR, 2.3 mg/mg) (Table 1). Further workup for suspected SLE and LN revealed positive ANA (>1: 320), high anti-dsDNA antibody titer (907.5 IU/mL), and triple aPL positivity (Table 2). Factor assays revealed factor II deficiency (41%; reference range, 70%–120%), whereas the other factors were normal. At this point, the initial diagnosis of IgAN was reclassified, as the patient fulfilled the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for SLE, with a score of 22, leading to a diagnosis of LN, along with APS and LAHPS (Table 3). Treatment with intravenous methylprednisolone pulse (30 mg/kg/dose for 3 days), followed by oral GC (prednisolone 2 mg/kg/day) and MMF (600 mg/m^2/dose twice daily) led to remission of proteinuria. GC was discontinued after 2 years, with MMF being continued. However, 2 years after cessation of GC, proteinuria worsened and did not improve despite reintroducing GC (prednisolone 1 mg/kg/day) and increasing the MMF dose up to 800 mg/m^2/dose twice daily. Rituximab (375 mg/m^2/dose, weekly, total 4 doses) induced an initial response, but nephrotic-range proteinuria relapsed. She is currently receiving monthly cyclophosphamide (500 mg/m^2/dose) in addition to

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Table 3. The 2019 European League Against Rheumatism/American College of Rheumatology criteria for SLE[a)]

Domain	Criteria	Weight	Upon IgAN diagnosis	Upon thrombotic event	Upon LAHPS diagnosis
Clinical domains					
Constitutional	Fever (>38 °C)	2	2	0	0
Hematologic	Leukopenia (<4,000/μL)	3	0	0	0
	Thrombocytopenia (<100,000/μL)	4	0	0	0
	Autoimmune hemolysis	4	0	0	0
Neuropsychiatric	Delirium	2	0	0	0
	Psychosis	3	0	0	0
	Seizure (generalized or partial/focal)	5	0	0	0
Mucocutaneous	Nonscarring alopecia	2	0	0	0
	Oral ulcers	2	0	0	0
	Subacute cutaneous lupus or discoid lupus	4	0	0	0
	Acute cutaneous lupus	6	0	0	0
Serosal	Pleural effusion or pericardial effusion	5	0	0	0
	Acute pericarditis	6	0	0	0
Musculoskeletal	Joint involvement	6	0	0	0
Renal	Proteinuria (>0.5 g/24 hr)	4	4	4	0
	Class II or V LN	8	0	0	0
	Class III or IV LN	10	0	0	10
Immunologic domains					
Antiphospholipid antibodies	Anticardiolipin antibodies or anti-β2GPI or LA	2	2	2	2
Complement	Low C3 or low C4	3	0	0	0
	Low C3 and low C4	4	0	0	4
SLE-specific antibodies	Anti-dsDNA antibody or anti-Smith antibody	6	6	0	6
Total score			14	6	22

SLE, systemic lupus erythematosus; IgAN, immunoglobulin A nephropathy; LAHPS, lupus anticoagulant-hypoprothrombinemia syndrome; LN, lupus nephritis; GPI, glycoprotein I; LA, lupus anticoagulant; C3, complement component 3; C4, complement component 4; dsDNA, double stranded DNA.

[a)]Patients are eligible for these criteria only if they have antinuclear antibodies positive at a titer of ≥1:80 or an equivalent positive test.

GC and MMF. Despite the introduction of cyclophosphamide, nephrotic-range of proteinuria (UPCR, 12.24 mg/mg) has persisted, along with a mild decrease in kidney function (estimated glomerular filtration rate 83.0 mL/min/1.73 m^2, calculated by the Schwartz equation 2012). However, the SLE activity markers have improved, recently normalizing (anti-dsDNA antibodies <0.1 IU/mL and C3/C4 125/19 mg/dL) at the last follow-up at age 15 years (Tables 1, 2). Additionally, no further thrombotic or bleeding events have occurred.

Discussion

The pathophysiology of LAHPS is not fully understood, although prothrombin–antiprothrombin antibody complexes are thought to play a key role [10]. Factor II deficiency in LAHPS is invariably associated with LA. Although the exact mechanism is unclear, studies suggest that aPL binding to factor II forms antigen-antibody complexes cleared by the reticuloendothelial system, leading to hypoprothrombinemia [10,11]. In general, LAHPS has a favorable prognosis with a mortality rate of <5%, but it poses the risk of potentially fatal hemorrhagic and thrombotic complications, with the former being more common [1,4]. Cases of fatal intracerebral hemorrhage and arterial thrombotic events, including ischemic stroke, have been reported, particularly in autoimmune disease-related LAHPS, such as SLE and APS, which is associated with worse prognosis and higher recurrence rates compared to infection-related LAHPS [1-4]. Moreover, triple aPL positivity, which was observed in our patient, had been strongly associated with recurrent thrombotic events in APS, further contributing to the risk [5]. Although APS commonly presents with recurrent miscarriages and thrombosis, hemorrhagic events occur in about 10% of cases. Therefore, LAHPS should be considered in APS patients presenting with bleeding or prolonged PT or aPTT [11]. While the mechanisms

of thrombosis in APS and LAHPS are not fully understood, they are distinct. APS is primarily mediated by anti-β2GPI antibodies, whereas LAHPS involves endothelial cell damage and platelet activation by LA [5,10]. In our patient, negative anticardiolipin and anti-β2GPI antibodies, along with positive LA, suggest that the thrombotic event was due to LAHPS associated with SLE, rather than APS. The subsequent bleeding event also appears to be due to LAHPS, likely attributable to hypoprothrombinemia. Although no specific cutoff value for factor II activity has been established for LAHPS, studies suggest a threshold below 50% to 60%, with median levels under 20%. One systematic review reported that 89% of patients with a factor II activity <50% experienced bleeding, consistent with our patient's level of 41% [1,4]. There are no standardized treatment guidelines for LAHPS. Corticosteroids are recommended as first-line therapy, with most patients responding well. Additional options, such as cyclophosphamide and rituximab, can be considered, as they were administered in our patient [1-4].

Delayed diagnosis and treatment of SLE can lead to progressive and irreversible organ damage. Early and accurate diagnosis, particularly of LN, is critical, because 5% to 20% of patients reportedly progress to kidney failure within 10 years [8]. However, early diagnosis of SLE can be challenging, as it presents a wide range of clinical symptoms that are often nonspecific or mild [12]. When SLE is suspected, close monitoring is essential even if the patient does not initially meet the diagnostic criteria.

Although IgAN with significant proteinuria is associated with unfavorable prognosis, LN poses a higher risk of recurrence, morbidity, and mortality and often requires long-term treatment and monitoring [7,8]. Differentiating IgAN from LN is crucial and challenging because of overlapping biopsy findings, such as mesangial hypercellularity and immune complex deposition, when other clinical clues are unclear. A full-house pattern is common in LN class IV, although dominant or co-dominant IgA staining can occur in both conditions [9]. Although IgAN is typically considered with synpharyngitic gross hematuria, LN can present similarly, and complement levels may not be markedly reduced in the early stages [7].

In our case, the initial kidney biopsy showed a membranoproliferative pattern, which is uncommon in IgAN (only 0.2% to 0.3%) but is more frequently observed in LN [9]. Moreover, idiopathic MPGN is uncommon in children, necessitating suspicion of other causes such as autoimmune diseases [13]. The coexistence of IgAN with an MPGN pattern suggests a more aggressive variant with a prognosis that is worse than that of typical IgAN, given that nephrotic syndrome is more common and predicts poorer kidney outcomes. Therefore, patients with severe clinical presentation and these histopathological findings can be misdiagnosed if there is no clinical suspicion of LN [7,14,15].

Our patient was initially diagnosed as IgAN with an MPGN pattern based on kidney biopsy, but notably met the 2019 EULAR/ACR criteria for SLE with a score of 14 upon initial presentation (Table 3). However, the diagnosis of SLE was missed and delayed because the patient was young, had nonspecific symptoms, and had inconclusive SLE-related laboratory profiles and histopathological findings. Immunosuppressive therapy, which was initially administered for IgAN, led to partial improvement of LN and complicated the diagnosis of SLE, which was ultimately confirmed during a flare after 10 months of discontinuing treatment. Although a repeat kidney biopsy was not performed, a retrospective review suggested that the histopathologic findings are compatible with LN class IV (Table 3). This case underscored the need for clinical suspicion for alternative diagnoses, such as LN, and the integration of clinical, serological, and histopathological findings rather than relying solely on histopathology in patients with glomerulonephritis presenting as IgAN. Furthermore, the importance of considering factor II testing and monitoring for rare complications, such as LAHPS, is highlighted, particularly in patients with SLE who have prolonged PT or aPTT.

Ethical statements

This report was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2408-121-1563). Informed consent was obtained from the patient and his parent, although this was a retrospective chart review study that involved no more than minimal risk.

Conflicts of interest

Hee Gyung Kang and Ji Hyun Kim are editorial board members of the journal but were not involved in the selection of peer reviewers, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article are reported.

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Author contributions

Conceptualization: HGK
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Investigation: CHL, JHK
Methodology: HGK, YHA
Visualization: HGK, YHA
Writing - original draft: CHL
Writing - review & editing: JHK
All authors read and approved the final manuscript.

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