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Diagnosis of Systemic Lupus Erythematosus During Medical Follow-up After Urinary Screening

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= Abstract =

A 16-year-old girl presented with proteinuria and microscopic hematuria detected through mass urinary screening and was diagnosed as having suspected postinfectious glomerulonephritis by renal biopsy. However, heavy proteinuria did not respond to angiotensin converting enzyme inhibitor therapy. After 6 months, cervical lymphadenitis developed and a neck node biopsy showed subacute necrotizing lymphadenitis. After an additional 2 months, she developed facial erythema and thrombocytopenia. A repeat renal biopsy demonstrated lupus nephritis class IV. She was treated with pulse methylprednisolone(500 mg/day intravenously for 3 consecutive days) followed by oral deflazacort and monthly intravenous cyclophosphamide pulse(1 g/m^2) for 6 months. We report a case diagnosed as systemic lupus erythematosus(SLE) during medical follow-up after urinary screening. **(J Korean Soc Pediatr Nephrol 2008;12:227-232)**

Key Words : Systemic lupus erythematosus(SLE), Lupus nephritis(LN)

INTRODUCTION

Systemic lupus erythematosus(SLE) is an autoimmune disease characterized by an overproduction of different autoantibodies and immune complex formation. Childhood-onset patients more often have nephropathy, fever, and lymphadenopathy[1]. The higher frequency of renal disease at onset in childhood-onset patients may contribute to the need for earlier aggressive treatment[2-4]. Nevertheless, it is not easy to diagnose SLE when a patient presents with only one or two criteria of SLE, which might also be overlapping symptoms of other diseases. Furthermore, an atypical presentation of childhood SLE is common, which may lead to a delay in diagnosis[1,5].

We report a case diagnosed as SLE during medical follow-up after urinary screening in a 16-year-old girl with suspected post-infectious glomerulonephritis.

CASE REPORT

A 16-year-old girl was referred to our hospital due to proteinuria and hematuria detected through mass urinary screening. The patient

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and her family had no remarkable medical history or symptoms. Her blood pressure was 115/65 mmHg and her chest X-ray, electrocardiogram, and abdominal ultrasonography were unremarkable. Initial laboratory findings were not remarkable except positive antinuclear antibody(ANA), abnormal urinary findings and positive serum mycoplasma antibody (Ab)(1:160). The laboratory findings of the patient are shown in Table 1.

At first, the patient fulfilled only 2 of 11 criteria of the American Rheumatism Association for SLE: renal disorder and antinuclear antibody. Renal biopsy showed endocapillary and mesangial proliferation under light microscopy(LM)(Fig. 1A). Global and segmental scleroses were observed in 6 and 4 glomeruli, respectively(Fig. 1B). The interstitium was diffusely widened by severe lymphoplasmacytic and neutrophilic infiltrate. Focal tubulitis and minimal atrophy were also observed. Immunofluorescence(IF) microscopy showed segmental granular IgG(++) and C3(+/-), staining along the peripheral capillary wall and granular deposits of IgG(++), C3(++), C4(+/-), and fibrinogen(+/-) in the mesangium(Fig. 1C). Electron microscopy(EM) showed mesangial expansion and swollen endothelium with subepithelial electron dense deposits, along with diffuse foot process effacement and intramembranous electron dense deposition(Fig. 1D). Because mycoplasma Ab

Table 1. Laboratory Findings

Date	5/2006	6/2006	10/2006	2/2007	3/2007	8/2007	10/2007
Clinical event	1st renal biopsy			2nd renal biopsy	1st CTx	6th CTx	After CTx
Serum/blood							
Hb(g/dL)	14.0	12.4	10.6	14.1	13.4	13.8	13.3
WBC($\times10^3$/L)	10.95	12.74	8.58	6.18	9.09	3.9	7.03
Lymphocyte	1.53	1.26	1.24	2.09	1.78	1.13	0.76
PLT($\times10^3/\mu$L)	153	107	151	75	141	205	184
C3(g/L) (0.83-1.46)	1.26	1.24		1.47	1.15	1.16	1.24
C4(g/L) (0.20-0.52)	0.33	0.37		0.34	0.28	0.31	0.35
Anti-dsDNA	Neg			Neg			
ANA	1:40+	1:40+		1:40+		1:40+	1:40
ANA pattern	mix	speck		speck		mix	
Anti-Ro(SS A)	Neg	Neg		+	Neg	Neg	
Anti-La(SS B)	Neg	Neg		Neg	Neg	Neg	
LAC	Neg	Neg		Neg	Neg	Neg	
ACL	Neg	Neg		+	+	Neg	
ESR(mm/hour)	51	45		32	18	23	16
Urine protein							
24 hr protein(g)	2.8	1.6		0.9	0.5		0.3

Abbreviations : CTx, chemotherapy; WBC, White blood cell count; PLT, Platelet count; Anti-dsDNA, Anti-double stranded DNA; ANA, Antinuclear antibodies; LAC, Lupus anticoagulant; ACL, Anticardiolipin antibodies; ESR, Erythrocyte sedimentation rate; Neg, negative; mix, mixed; speck, speckled

was positive, she was given enalapril(7.5 mg/day) and oral Roxithromycin(150 mg/day), but proteinuria and hematuria persisted.

After 6 months, her heavy proteinuria persisted at 1.8 g/day and creatinine clearance was 52.79 ml/min. There was no interval change in mycoplasma Ab(1:160). We started Deflazacort(72 mg/day) and stopped enalapril due to a decreased glomerular filtration rate. She subsequently developed right cervical lymphadenitis with fever and neck node biopsy revealed subacute necrotizing lymphadenitis.

After two more months, she developed a malar rash and her platelet count decreased to 86×10^3 per microliter. Repeated immunologic assays were positive in anti-cardiolipin Ab, anti SS-A/Ro Ab and VDRL. At this point, she fulfilled 5 of 11 criteria of the American Rheumatism Association for SLE: malar rash, renal disorder, antinuclear Ab, hematologic disorder (thrombocytopenia), and immunologic disorder. Second renal biopsy was performed 9 months after the first biopsy. Nine of 35 glomeruli(26%) were globally sclerotic and 17 (49%) showed synechia to Bowman's capsule. Mesangial proliferation was persisted and the glomerular basement membrane was thickened. The tubules show mild atrophy. Interstitial inflammation was diffuse and severe(Fig. 2A).

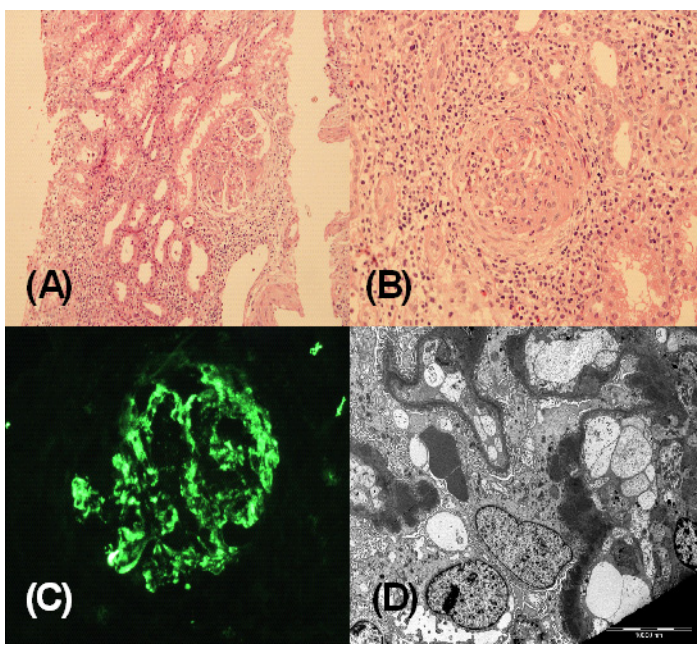

Fig. 1. (A) The first renal biopsy findings. Renal biopsy shows endocapillary and mesangial proliferation, and the interstitium is diffusely widened by severe lymphoplasmacytic and neutrophilic infiltrate(×100). (B) Segmental sclerosis is observed(×200). (C) Immunofluorescence microscopy shows segmental granular deposition of IgG(++) along the peripheral capillary wall and in the mesangium(×400). (D) Electron microscopy shows mesangial expansion, swollen endothelium with subepithelial electron dense deposits, diffuse effacement of foot process and intramembranous electron dense deposition.

IF microscopy showed no glomeruli. EM revealed subepithelial electron dense deposits, increased mesangial matrix, basement membrane thickening, and focal foot process effacement(Fig. 2B). Findings of the second biopsy led to a diagnosis of class IV lupus nephritis(LN), and she was treated with pulse methylpredinisolone(500 mg/d intravenously for 3 consecutive days), followed by oral deflazacort and monthly intravenous cyclophosphamide pulse(1 g/m^2) for 6 months.

After cyclophosphamide pulse therapy, 24hr urinary protein levels decreased, platelet count increased, and anti-cardiolipin and anti SS-A/Ro Abs were negative.

DISCUSSION

In this report, we describe a female patient with SLE who initially presented with proteinuria and hematuria. Initial renal biopsy revealed suspected postinfectious glomerulonephritis.

Renal involvement in SLE is known to present as a variety of morphological lesions. However, certain features are usually found only in LN, such as a fullhouse IF pattern (i.e., simultaneous detection of IgA, IgG, IgM, C1q, and C3 deposits), cytoplasmic tubuloreticular inclusions(TRI) on EM, and membranous nephropathy with mesangial deposits[6]. Gianviti et al.[7] reported three patients who presented with a glomerulopathy suggestive of LN without any other clinical findings of SLE. Nakahara et al[8]. reported an 11-year-old girl who was found to have proteinuria by mass urinary screening and developed SLE 21 months later. They concluded that endothelial TRI on EM is a more significant early sign of SLE than "full-house" IF pattern, especially in pediatric cases. We reviewed the first renal biopsy findings again. There was no full-house IF pattern, but we could not absolutely rule out LN based on pathologic findings.

In Korea, we perform annual mass urinary screenings so we can detect hematuria or proteinuria relatively early before patients develop clinical symptoms of lupus.

After 6 months, our patient presented with cervical necrotizing lymphadenitis. It has been reported that Kikuchi's disease(KD)-like lymphadenitis occurs in SLE patients[9]. The co-

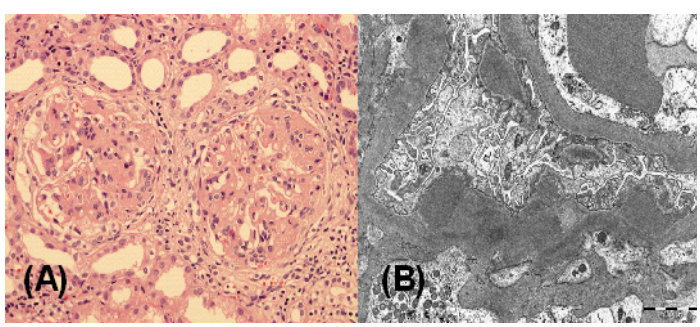

Fig. 2. (A) The second renal biopsy findings. The glomeruli are globally sclerotic and show synechia to Bowmans capsule. (B) Electron microscopy shows subepithelial electron dense deposits and increased mesangial matrix, basement membrane thickening and focal effacement of foot process.

existence of lymphadenitis with SLE is mainly seen in necrotizing type KD. So the possibility of SLE should always be considered if a lymph node looks like the necrotizing type of KD.

The laboratory finding of this patient needs differentiation from some other connective tissue disease. Especially positive finding in anti SS-A/Ro Ab, antinuclear Ab can suggest Sjogren syndrome. The diagnosis of Sjogren syndrome is based on clinical features supported by biopsy of lip or glands but this patient had no ocular or oral symptom related to exocrine disease.

And Arbuckle et al.[10] investigated the onset and progression of autoantibody development before clinical diagnosis. They reported that some autoantibodies(antinuclear, anti-Ro, anti-La, and antiphospholipid Abs) usually precede the onset of SLE by many years. Others(anti-Sm and antinuclear ribonucleoprotein Abs) typically appear only months before diagnosis[10,11].

In conclusion, the presenting manifestations of SLE in children are diverse[12], so if abnormal urinalysis and renal pathologic findings are persistent, LN should be kept in mind, and urinalysis and immunologic markers should be serially monitored to avoid a delay in diagnosis. If abnormal immunologic findings are found on follow-up, patients should be routinely evaluated for the emergence of clinical features. Because delayed diagnosis of SLE might lead to an unfavorable outcome, early detection and treatment with steroidal and/or immunosuppressive agents may be important to minimize organ damage in children with LN.

한 글 요 약

학교 집단 요 검사 이상으로 추적검사 중 전신 홍반 루푸스로 진단된 1예

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16세 여아가 학교 소변 검사에서 단백뇨와 현미경적 혈뇨가 나타났으며 신생검에서 감염 후 사구체 신염으로 추정되었다. 그러나 단백뇨는 안지오텐신 효소 억제제 치료에도 반응하지 않았다. 6개월 후 경부 림프절염이 나타났고 목 주위 림프절 생검에서 아급성 괴사성 림프절염 소견을 보였다. 이후 2개월 후, 환아는 얼굴의 발진과 혈소판 감소증을 보였다. 재 신생검에서 루프스 신염 class IV 소견을 보였다. 환아는 충격 methylprednisolone (500 mg/일) 3일간 정주 후 경구 deflazacort로 유지하였으며, 이와 함께 cyclophosphamide(1 g/m^2)를 월 1회 정주 충격 요법을 6회 실시하였다. 이에 본 저자들은 학교 집단 요 검사 이상으로 추적검사 중 전신 홍반 루푸스로 진단이 되었던 증례를 보고하는 바이다.

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