A Rare Case of Systemic Lupus Erythematosus Applying to the Family Medicine Outpatient Clinic with Periorbital Edema

Tuğba Arpa, Ayşen Kutan Fenercioğlu, Nurver Turfaner Sipahioğlu

Department of Family Medicine, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

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Abstract

Systemic lupus erythematosus may present with different clinical signs such as fatigue, fever, dermatitis, photosensitivity, alopecia, arthritis, serositis, hematological abnormalities, mucosal ulcerations, Raynaud phenomenon, neurological disease, and glomerulonephritis. Rarely, kidney involvement with the absence of antinuclear antibody (ANA) positivity may be the first and only finding in systemic lupus erythematosus. Since renal involvement affects prognosis negatively, delays in diagnosis and treatment can cause an increase in mortality and morbidity. In this article, we presented an interesting case of systemic lupus erythematosus, who applied to the family medicine outpatient clinic with periorbital edema in whom we considered renal involvement and determined histopathological findings that were compatible with lupus nephritis despite the absence of ANA positivity.

Keywords: Edema, primary care, systemic lupus erythematosus

Aile Hekimliği Polikliniğine Periorbital Ödemle Başvuran Nadir Bir Sistemik Lupus Eritematozis Vakası

Öz

Sistemik lupus eritematozus yorgunluk, ateş, dermatit, fotosensitivite, alopesia, artrit, serözit, hematolojik anormollikler, mukozal ülserasyonlar, Raynaud fenomeni, nörolojik hastalık ve glomerülonefrit gibi farklı klinik bulgularla başlayabilir. Sistemik lupus eritematozusta nadiren ANA pozitifliği olmadan var olan böbrek tutulumu ilk ve tek bulgu olabilir. Renal tutulum prognozu olumsuz etkilediğinden tanı ve tedavideki gecikmekler mortalite ve morbidite artışına neden olmaktadır. Çalışmamızda, Aile Hekimliği polikliniğine periorbital ödemle başvuran ve böbrek tutulumu düşünerek yaptığımız ileri tetkiklerde histopatolojik bulguları, ANA ve anti-dsDNA negatif olduğu halde, lupus nefritiyle uyumlu olan ilginç bir Sistemik Lupus Eritematozus vakasını sunduk.

Anahtar kelimeler: Sistemik lupus eritematozus, ödem, birinci basamak

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology, characterized by the development of antibodies against various nuclear and cytoplasmic antigens [1]. According to the criteria determined by the American Rheumatology Association, 4 of 11 criteria, consisting of malar rash, discoid rash, photosensitivity, ulcers in the mouth, arthritis, serositis, renal disorder, neurological disorder, hematological disorder, immunological disorder, and abnormal antinuclear antibodies make the diagnosis of SLE [2]. There are 3 classification sets for SLE other than the 1982 revised criteria for the classification of SLE.These are the 2019 European League Against Rheumatism/American College of Rheumatology (ACR) criteria, 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, and 1997 ACR criteria [3, 4]. According to the SLICC rule for the classification of SLE, the patient must satisfy at least 4 criteria, including at least one clinical criterion and one immunologic criterion OR the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti-double-stranded DNA (ds-DNA) antibodies (Table 1) [4]. Renal involvement is the first finding in approximately 50% of the patients. Lupus nephritis is used primarily to express the glomerular damage caused by SLE, and 55% of its symptoms is proteinuria [3]. Renal involvement is a common complication of SLE with an increased risk of mortality and morbidity [4]. In this article, we presented an interesting case of SLE who applied to the family medicine outpatient clinic with periorbital edema in whom we considered renal involvement and determined histopathological findings that

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Address for Correspondence/Yazışma Adresi: Ayşen Kutan Fenercioğlu, Department of Family Medicine, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
E-mail/E-posta: aysenfenerci@hotmail.com
aysen.fenercioglu@istanbul.edu.tr

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Table 1. The Systemic Lupus International Collaborating Clinics Criteria [4]

Clinical criteria
1. Acute cutaneous lupus including
Lupus malar rash (do not count if malar discoid)
Bullous lupus
Toxic epidermal necrolysis variant of SLE
Maculopapular lupus rash
Photosensitive lupus rash in the absence of dermatomyositis
or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus including classical discoid rash
Localized (above the neck)
Generalized (above and below the neck)
Hypertrophic (verrucous) lupus
Lupus panniculitis (profundus)
Mucosal lupus
Lupus erythematosus tumidus
Chillblain lupus
Discoid lupus/lichen planus overlap
3. Oral ulcers:
Palate
Buccal
Tongue
or nasal ulcers
In the absence of other causes, such as vasculitis, Behcet's disease, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia
5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and 30 minutes or more of morning stiffness
6. Serositis
Typical pleurisy for more than 1 day
or pleural effusions
or pleural rub
Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
or pericardial effusion
or pericardial rub
or pericarditis by EKG in the absence of other causes, such as infection, uremia, and Dressler's pericarditis

Table 1. The Systemic Lupus International Collaborating Clinics Criteria [4] (Continued)

7. Renal
Urine protein/creatinine (or 24-h urine protein) representing 500 mg of protein/24 h
or
Red blood cell casts
8. Neurologic
Seizures
Psychosis
Mononeuritis multiplex in the absence of other known causes such as primary vasculitis
Myelitis
Peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
Acute confusional state in the absence of other causes, including toxic-metabolic, uremia, drugs
9. Hemolytic anemia
10. Leukopenia (< 4,000 mm^{-3} at least once) in the absence of other known causes such as Felty's, drugs, and portal hypertension
or
Lymphopenia (< 1,000 mm^{-3} at least once) in the absence of other known causes such as corticosteroids, drugs, and infection
11. Thrombocytopenia (<100,000 mm^{-3}) at least once in the absence of other known causes such as drugs, portal hypertension, and TTP
Immunological Criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody: any of the following lupus anticoagulant
False-positive RPR
Medium or high titer anticardiolipin (IgA, IgG, or IgM)
Anti-β2 glycoprotein I (IgA, IgG, or IgM)
5. Low complement
Low C3
Low C4
Low CH50
6. Direct Coombs test in the absence of hemolytic anemia

*Criteria are cumulative and need not be present concurrently.

were compatible with lupus nephritis despite the absence of antinuclear antibody (ANA) positivity. The presence of biopsy-proven lupus nephritis is sufficient to diagnose a patient as SLE according to the SLICC criteria. However, different from the SLICC criteria, ANA and/or ds-DNA was negative in this patient.

Table 2. Laboratory findings

HGB	10.2 g/dL	Glucose	75 mg/dL
HCT	27.7	Creatinine	0.59 mg/dL
WBC	4400 μL^{-1}	Potassium	4 mmol/L
MCV	86 fL	Calcium	7.64 mg/dL
Plt	156.000 μL^{-1}	TSH	4.75 µIU/mL
Lenfocytes	1900 μL^{-1}	AST	26 U/L
CRP	8.2 mg/L	ALT	19 U/L
Ferritin	144.5 ng/mL	Free T4	1.12 ng
Total protein	4.3 g/dL	Albumin	2.6 g/dL
C3	0.47 g/L	C4	0.05 g/L
Proteinuria	6.5 g/day	Albuminuria	4.9 g/day

Hgb: hemoglobin; Hct: hematocrite; WBC: white blood cells; MCV: mean corpuscular volume; Plt: platelets; CRP: C-reactive protein; TSH: thyroid stimulating hormone; C3: complement 3; C4: complement 4

Figure 1. Periorbital edema

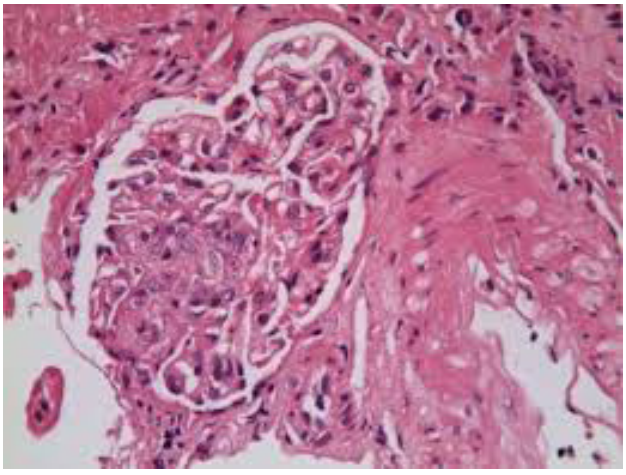

Figure 2. Histopathological findings

Case Presentation

An 18-year-old girl applied to our clinic with puffy eyes, ankle edema, difficulty in walking, and decline in school performance. These complaints had started 2 weeks ago after a throat infection. Other than these complaints, she did not have any other symptom determined by clinical criteria of SLICC. In her medical history, there was asthma that was under control for 6 years without medical treatment. There was no history of smoking neither alcohol use. Her family history did not include any abnormalities.

On physical examination, the general condition of the patient was good; she was cooperative and oriented. Her physical examination revealed the following: blood pressure: 130/80 mm/Hg, fever: 36.7^{0}C, body mass index: 25.9 kg/m^2, and periorbital edema, pretibial edema: +/+ in both feet; there was not any other pathological features in other system examinations (Figure 1). The laboratory findings of the patient were as follows: hemoglobin: 10.2 g/dL, hematocrit: 27%, lymphocyte: 1900 μL^{-1}, white blood cell count: 4,400 μL^{-1}, mean corpuscular volume: 86 fL, platelet count: 156,000 μL^{-1}, glucose: 75 mg/dL, creatinine: 0.6 mg/dL, K: 4 mmol/L, calcium: 7.64 mg/dL, P: 5.8 mg/dL, AST: 26 U/L, ALT: 19 U/L, total protein: 4.3 g/dL, albumin: 2.6 g/dL, total cholesterol: 267 mg/dL, triglyceride: 165 mg/dL, LDL: 213 mg/dL, HDL: 41 mg/dL, C-reactive protein: 8 mg/L, thyroid stimulating hormone: 4.7 µIU/mL, and free T4: 1.12 ng/dL (Table 1). Abnormalities in her blood tests included decrease in total protein and albumin levels, anemia, and hyperlipidemia (Table 2).

Urinalysis revealed two positive proteins and one positive erythrocyte. Urine sedimentation revealed 1 leukocyte, 14 erythrocytes, 2 squamous cells, 2 hyalene cylinders, and 1 granular cylinder. Her 24-h urinalysis revealed 6.5 g/day proteinuria and 4.9 g/day albuminuria.

Her blood complement levels were low (C3: 0.47 g/L and C4: 0.05 g/L). ANA, anti-ds-DNA, p-ANCA, c-ANCA, anti-RNP antibody, anti-SSA antibody, anti-SSB antibody, anti-sm antibody, anticardiolipin antibody, and rheumatoid factor levels were normal. T-negativity in all precordial leads was detected in electrocardiography (ECG). Echocardiography demonstrated left ventricular functional abnormality (global hypokinesia), moderate mitral insufficiency, and low ejection fraction. Her abdominal ultrasonography was normal.

Our initial diagnosis was nephrotic syndrome. She was referred to nephrology clinic for a renal biopsy. Her renal biopsy revealed widespread prominent neutrophil infiltration and focal fibrinoid necrosis in glomeruli under light microscopy suggesting nephrotic syndrome (Figure 2). Immunofluorescent analysis demonstrated "full house nephropathy" with IgA, IgG, IgM, C1q, and C3 immune deposits in glomerulus observed in lupus nephritis.

As the histopathological findings strongly suggested lupus nephritis, the patient was diagnosed as SLE-related nephrotic syndrome and started the treatment with mycophenolate mofetil 2 g/day, prednisolone 60 mg/day, hydroxychloroquine sulfate 400 mg/day, ramipril 2.5 mg/day, enoxaparin sodium 6,000 IU/0.6 mL, and vitamin D.

Written informed consent was obtained from the patient who participated in this study.

Discussion

SLE is a systemic autoimmune disease, which is characterized by the development of antibodies against various nuclear and cytoplasmic antigens that can affect many organs, especially the skin, kidney, lung, heart, hematopoietic system, and brain [5].

SLE occurs mostly between the ages of 20 and 40 and is 9 times more common in women than in men. The incidence of lupus nephritis is 0.36–0.9/100,000 and its prevalence is 1/2,000 [6].

SLE is usually presented with extrarenal findings. Multisystemic involvement accompanying renal involvement is generally not correlated with the presence and severity of renal lesions. Renal involvement potentially correlates with urinary changes and serological findings [7]. The presence of biopsy-proven lupus nephritis is sufficient to diagnose a patient as SLE according to the SLICC criteria. However, different from the SLICC criteria, ANA and/or ds-DNA was negative in this patient. In contrast, ankle swelling and tenderness in both feet, proteinuria, and anemia were compatible with clinical criteria, and low C3 and C4 levels were compatible with immunologic criteria.

Clinical renal manifestations of SLE can be classified into 6 different types: telescopic urine (proteinuria predominantly), acute or chronic renal failure, acute nephritic syndrome, rapid progression glomerulonephritis, nephrotic syndrome and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome such as thrombotic microangiopathies, anticardiolipin syndrome, renal vein thrombosis, and superimposition of malignant hypertension [8, 9].

In a study reported by Keni et al., it was observed that the patients with renal involvement had less involvement of the skin, skeletal–muscular system, and constitutional symptoms, and greater involvement of the hematological system and gastrointestinal tract [10-12].

Cardiac involvement is another important cause of morbidity and mortality in SLE. All anatomic structures of the heart may be affected in SLE patients. Pericarditis is part of the diagnostic criteria of ACR and SLICC. Accelerated atherosclerosis leading to premature coronary artery disease, myocardial involvement, and valvular heart disease with abacterial endocarditis have been all described in SLE [13]. Although various methods, including cardiovascular magnetic resonance, have been used in order to diagnose cardiac involvement in SLE, we tested our patient only with ECG and echocardiography because she was asymptomatic in terms of cardiac involvement. Repolarization abnormalities were defined as T-wave inversions in her ECG, and her echocardiography demonstrated left ventricular functional abnormality (global hypokinesia), moderate mitral insufficiency, and low ejection fraction. No evidence supporting pericarditis was detected in her echocardiography.

Although rheumatological diseases such as SLE are mostly diagnosed and followed up by the secondary and tertiary healthcare physicians, the patients who apply with the complaint of edema to their primary care physicians should be evaluated in terms of the findings that may be accompanied and can then be referred to the rheumatology and nephrology specialists.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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References

1. Bagavant H Deshmukh US, Gaskin F, Fu SM. Lupus glomerulonephritis revisited 2004: autoimmunity and end-organ damage. Scand J Immunol 2004; 60: 52-63. [CrossRef]
2. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-7. [CrossRef]
3. Aringer M. EULAR/ACR classification criteria for SLE. Semin Arthritis Rheum 2019; 49: 14-7. [CrossRef]
4. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of systemic lupus international collaborating clinics classification criteria for systemic lupus Erythematosus. Arthritis Rheum 2012; 64: 2677-86.
5. Gianviti A, Barsotti P, Barbera V, Faraggiana T, Rizzoni G. Delayed onset of systemic lupus erythematosus in patients with "full-house"nephropathy. Pediatr Nephrol 1999; 13: 683-7. [CrossRef]
6. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004; 65: 521-30. [CrossRef]
7. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725. [CrossRef]
8. Tsao BP. Genetic susceptibility to lupus nephritis. Lupus 1998; 7: 585-90. [CrossRef]
9. Berden JHM. Lupus nephritis: Nephrology forum. Kidney Int 1997; 52: 538-58. [CrossRef]
10. Kiremitçi S, Ensari A. Recent Developments in the Pathogenesis of Lupus Nephritis. Turk Neph Dial Transpl 2014; 23: 175-80. [CrossRef]
11. Luzar B, Ferluga D. Role of lipids in the progression of renal disease in systemic lupus erythematosus patients. Wien Klin Wochenschr 2000; 112: 716-21.
12. Keni M, Koca N, Ersoy A. The Comparison of Lupus Patient's Characteristics with or without Renal Involvement on Administration. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2012; 38: 79-83.
13. Burkard T, Trendelenburg M, Daikeler T, Hess C, Bremerich J, Haaf P, et al. The heart in systemic lupus erythematosus- A comprehensive approach by cardiovascular magnetic resonance tomography. PLoS One 2018; 13: e0202105. [CrossRef]