CASE REPORT OLGU SUNUMU

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Antiphospholipid Syndrome with Systemic Lupus Erythematosus as the Cause of Recurrent Strokes: A Case Report and Literature Review

Tekrarlayan İnmelerin Nedeni Olarak Sistemik Lupus Eritematozusun Eşlik Ettiği Antifosfolipid Sendromu: Olgu Sunumu ve Literatür Taraması

Kerim DEMİRSÖZ[a], Güldal Funda YÜZER NAKİPOĞLU[a], Cemile Sevgi POLAT[a]

[a]Clinic of Physical Medicine and Rehabilitation, Ankara Bilkent City Hospital Ankara, Türkiye

ABSTRACT Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are autoimmune diseases and are associated with an increased risk of cerebrovascular disease. APS can be primary but it is mostly seen in conjunction with SLE. Stroke is usually seen within the first 5 years from diagnosis of SLE but it rarely occurs as the initial manifestation of SLE. Underdiagnosis of SLE causes recurrent strokes, increases in morbidity and mortality. The present case is a 64-years-old male patient who had 4 strokes in 3 years and is subsequently diagnosed with APS and SLE in our clinic. In conclusion, SLE should always be in our mind during etiologic investigation of stroke in order to decrease the risk of recurrence by means of secondary prevention.

Keywords: Systemic lupus erythematosus; antiphospholipid syndrome; recurrent strokes; elderly male patient

ÖZET Sistemik lupus eritematozus (SLE) ve antifosfolipid sendromu [antiphospholipid syndrome (APS)] otoimmün hastalıklardır ve artmış serebrovasküler hastalık riski ile ilişkilidir. APS birincil olabilir, ancak çoğunlukla SLE ile birlikte görülür. İnme genellikle SLE tanısından sonraki ilk 5 yıl içinde görülür, ancak nadiren SLE'nin ilk belirtisi olarak ortaya çıkar. SLE'nin yetersiz teşhisi, tekrarlayan inmelere, morbidite ve mortalitede artışa neden olur. Bu olgu 64 yaşında, 3 yılda 4 kez inme geçiren ve daha sonra kliniğimizde APS ve SLE tanısı alan erkek hastadır. Sonuç olarak inme etiyolojik araştırmalarında, sekonder koruma ile rekürrens riskini azaltmak için SLE her zaman aklımızda olmalıdır.

Anahtar Kelimeler: Sistemik lupus eritematozus; antifosfolipid sendromu; rekurren inme; yaşlı erkek hasta

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease and the nervous system is one of the major systems affected in patients with SLE. Neurological involvement in SLE, termed neuropsychiatric lupus [Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)] leads to increased rates of morbidity and mortality.[1] Cerebrovascular disease affects between 8% and 15% of patients with SLE but rarely occurs as the primary manifestation.[1,2] The risk of stroke among patients with SLE is twofold to threefold higher compared with the general population and the risk of recurrence is very high after a cerebrovascular disease.[3,4] Ischemic stroke is the most common form of cerebrovascular disease. Major factors implicated in the higher stroke incidence in SLE patients are higher burden of cerebral small vessel disease, antiphospholipid syndrome (APS) and thrombosis, accelerated atherosclerosis and vasculitis.[1] SLE-related stroke is more frequently, observed among young patients, especially women.[2]

Correspondence: Cemile Sevgi POLAT
Clinic of Physical Medicine and Rehabilitation, Ankara Bilkent City Hospital Ankara, Türkiye
E-mail: drsevgipolat@hotmail.com

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APS is associated with antibodies, including lupus anticoagulant, anticardiolipin antibodies and anti-β2-glycoprotein 1 antibodies and causes arterial or venous thrombosis, and pregnancy morbidity. APS occurs in isolation, it is much more prevalent in patients with SLE than in the general population. Antiphospholipid antibodies are common in patients with SLE and increase the risk of cerebrovascular disease.[1]

Here, we present a 64 year-old male patient with a stroke who admitted to our clinic for rehabilitation, then diagnosed with APS and SLE in our clinic. We underline the importance of diagnosis of SLE in stroke patients in prevention of recurrence.

CASE REPORT

A 64-year-old male patient was admitted to our stroke rehabilitation unit with the complaints of weakness in the both upper and lower extremities, balance disability and inability to speak. The patient had a history of recurrent strokes (4 ischemic strokes in 3 years) and arterial hypertension. His medication was including calcium channel blocker, angiotensin II receptor antagonist, and antiplatelets (dipyridamole 75 mg and clopidogrel 75 mg), all once daily. His mother had arterial hypertension and history of stroke. On neurological examination, the patient had bilateral hemiplegia with no sitting balance and had Broca's aphasia.

In the etiologic investigation of stroke, there were no abnormalities in the cardiological (electrocardiography, ecocardiography and holter monitoring) and Doppler ultrasonographic examination (carotid and vertebral arterial systems,venous system of the lower extremities). Primarly lipid profile and homocysteine level, then vasculitic and genetic panels were tested (Table 1, Table 2). Some of the test re-

TABLE 1: Laboratory test results (lipid profile and homocysteine).

Test	Result	Unit	Normal interval	Low/normal/high
Total cholesterol	182	mg/dL	<200	Normal
Trigliseride	176	mg/dL	<150	**High**
HDL cholesterol	32	mg/dL	40<	Low
LDL cholesterol	107	mg/dL	<100	**High**
VLDL	35	mg/dL	10-40	Normal
Non-HDL cholesterol	142	mg/dL	<130	
Homocysteine	20,7	µmol/L	5-12	**High**

HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein.

TABLE 2: Laboratory test results (Vasculitic and genetic panel).

Test	Result	Unit	Normal interval	Low/normal/high
Protein S activity	65.7			Low
INR	1.12			
aPTT	27.8			
Factor 5 (proaccelerin)	33	%	70-120	Low
Factor 8	287			High
Factor 10 (stuart prower)	51	%	70-120	Low
ANA (titer 1)	1/320 (positive 2+)			**Positive**
ANA (titer 2)	1/320 (positive 2+)			**Positive**
Anti Ro-52 (immunoblotting)-	Borderline positive			
Lupus anticoagulant scan	1.26		<1.2	**High**
Lupus anticoagulant verification test	1.34		<1.2	**High**
Anti-thrombin III activity	73.9			Low
Anti-thrombin III antigen	0.18	g/L	0.23-0.37	Low
Anti-ds DNA	137.83	RU/mL	<100	**High**

INR: International normalized ratio; aPTT: Activated partial thromboplastin time.

sults are not involved in the table including collagen EPI, collagen ADP, protein C activity, protein C antigen, protein S antigen, active protein C resistance, prothrombin activity, prothrombin time, factor 7 (proconvertin), factor 9 (christmas), factor 11 (plasma thromboplastin), factor 12 (hagemann), factor 13 (fibrin stabilising factor), C3c, C4, beta-2 glycoprotein I immunoglobulin (Ig)A, beta-2 glycoprotein I IgM and beta-2 glycoprotein I IgG. They were within the normal range. Also anti-Sm (immunoblotting) E, anti nRNP/Sm (immunoblotting)-E, anti SS-A (immunoblotting)-E, anti SS-B (immunoblotting)-E, anti Scl-70 (immunoblotting)-E, anti-Jo1 (immunoblotting)-E, p ANCA-IFA, c ANCA-IFA, MPO ANCA-IFA and PR3 ANCA-IFA tests were also negative.

As seen in the table, alongside many other tests, lupus anticoagulant, anti-ds DNA, and ANA were positive. During hospitalization, we observed oral ulcers on physical examination. His complete urine analysis reported with 2+ proteinuria and urine microscopy with granular cylinders. Twelve weeks later, APS antibodies were tested again. The results were positive for lupus anticoagulant and negative for anticardiolipin and anti-beta-2 glycoprotein I antibodies. Thus, the diagnosis of SLE was established, according to the Systemic Lupus International Collaborating Clinics Classification criteria (Table 3).[5] Then, the patient was consulted to the department of rheumatology in terms of treatment of SLE. Warfarin, glucocorticoid, and hydroxychloroquine sulfate medication started to be given the patient. International normalized ratio was kept over 3.0 to avoid recurrent strokes. Renal biopsy was planned to detect the type of lupus nephritis.

Written informed consent was obtained from the patient for publication of this case report.

DISCUSSION

A case presenting with recurrent strokes due to SLE was discussed in this case report. Our patient had 4 strokes in 3 years and an etiologic cause was not able to be found in previous hospitalizations. Etiologic investigation of stroke is crucial in the prevention of recurrent strokes. The initial etiologic workup includes Doppler ultrasonographic examination of carotid and vertebral arterial systems and cardiological (electrocardiography, ecocardiography and holter monitoring) examination to eliminate thromboembolic cause. Investigation includes hypercoagulable situations, vasculitis, and rheumatological disorders in younger patients.[6] In older patients, this may be overlooked but recurrent strokes or unknown etiology should be a reminder for us. Vascular and genetic disease panels can also be checked if the previous tests are reported normal. Because of short hospitalization periods due to economical issues, all those tests may not be completed. This may lead to recurrent strokes, increase in morbidity and mortality.

Stroke is one of the most serious symptom of SLE and affects between 8% and 15% of patients with SLE.[1] The risk of recurrence is very high after a cerebrovascular disease in patients with SLE.[4] In a systematic review of Zhang et al., the ratio of cerebrovascular disease in patients with SLE is found %12.3, and 54.6% of stroke patients were found to have a recurrent stroke, leading to 58.7% morbidity and a 26.8% mortality rate.[7] Our patient had 4 strokes in 3 years and his neurologic and cognitive functional status has regressed with every stroke. The patient had bilateral hemiplegia, with balance disability and had Broca's aphasia. We determined the high ratio of recurrence and the effects of recurrence on morbidity in our case.

In the literature, it has been reported that patients with SLE have more comorbid conditions which are also risk factors for stroke such as vasculitis, antiphospholipid syndrome, and hypertension.[4] As reported in the literature, our patient had APS and hypertension as risk factors for stroke.

Stroke rarely occurs as the initial manifestation of SLE and most often affects young women.[2] Contrary to this literature, our patient was man and was not young. Maybe for this reason, in our patients underlying SLE in the occurence of stroke was not considered in previous hospitalizations.

APS can be primary or can be seen in conjunction with other diseases, mainly SLE.[1] Anticardiolipin, anti-beta-2 glycoprotein I (β2GPI), and lupus anticoagulant are 3 main antibodies need to be checked in APS. Diagnosis of APS requires at least

TABLE 3: Clinical and Immunologic Criteria Used in the Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria.

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, chillblains lupus, discoid lupus/lichen planus overlap
3. Oral ulcers: palate, buccal, tongue or nasal ulcers in the absence of other causes, such as vasculitis, Behcets, 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 2 or more joints, characterized by swelling or effusion or tenderness in 2 or more joints and thirty 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
7. Renal Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr 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.

SLE: Systemic lupus erythematosus; EKG: Electrocardiography; Ig: Immunoglobulin; RPR: Rapid plasma reagin.

one laboratory positivity and one clinical symptom (Table 4).[8] Laboratory positivity should be shown 2 times with 12 weeks between the tests.[8] Appropriate treatment is the mainstay of avoiding recurrent strokes. We checked for APS antibodies after the initial etiologic tests of investigation of stroke. Lupus anticoagulant was positive at initial tests. Twelve weeks later, it was positive again. Antibody positivity with recurrent strokes made us to diagnose the patient with APS.

Shih et al. reported a case who is a 47 years old female patient previously diagnosed with SLE.[9] After the stroke, the patient was also diagnosed with APS. She was treated with 100 mg acetylsalicylic acid and 5 mg warfarin daily for secondary prevention. Like this case, in our patient, APS was noticed after the stroke. In his previous strokes due to overlooking the diagnosis and not starting the treatment, he had recurrent strokes.

A patient was reported by Ioannidis et al., 37 years old man with a history of rheumatoid arthritis and hypothyroidism.[2] Patient's mother was also diagnosed with SLE. The patient had acute dizziness, left hemiataxia, and gait ataxia. Magnetic resonance imaging (MRI) showed acute ischemic lesion for left superior cerebellar artery. Tests showed the patient was positive for anti-ds DNA, anti-SSA, and lupus coagulant. High dose intravenous (IV) corticosteroid, hydroxychloroquine, IV heparin followed by acenocoumarol were the main treatments. The patient didn't have further events for the next 12 months. Contrary to this case report, our patient did not have any other rheumatologic disease and there was no family history of rheumatologic disease. But the diagnosis of SLE and APS was done after the stroke, similar to this case. Our patient could not receive appropriate treatment because he was not diagnosed with SLE in his previous strokes, thus he had recurrent strokes. It is important to make the diagnosis as early as possible for an appropriate medical treatment. Clinicians should be aware of the diagnosis of SLE in recurrent strokes.

The most common MRI findings of NPSLE are cortical atrophy, ventricular dilation, cerebral edema, diffuse white matter abnormalities, focal atrophy, cerebral infarction, and acute leukoencephalopathy.[4] Several case reports about ischemic stroke as initial manifestation of SLE has been reported in the literature.[2] In these previous reports, it was determined that ischemic infarcts were more common in posterior circulation (vertebrobasilar system and branches) territory of cerebrum and the pons was the most affected area. Cranial MRI of our patient was reported with paranchymal atrophy caused 3rd and 4th ventricular dilatation, cerebellar intensity degeneration, brainstem atrophy, diffuse gliosis in pons, and perifocal gliosis in bilateral frontal lobes. Consistent with the literature, posterior circulation territory was more affected and we considered that due to recurrent strokes, both anterior (carotis system and branches) and posterior (vertebrobasilar system and branches) circulation territory were affected in our patients.

Kwon et al. also reported 2 women patients aged 16 and 26 who were diagnosed with SLE after having strokes.[10] A 16-years old patient had a dull headache, action tremor, and quadriataxia. MRI showed vertebrobasilar infarcts, and left lateral pons lesions. The patient was treated with oral anticoagulation and cyclophosphamide. In the next follow ups of 3 years, the patient had no new cerebrovascular events. A 26-years-old patient had also headache, dysarthria, and quadriataxia. MRI showed vertebrobasilar infarct

TABLE 4: Antiphospholipid Syndrome Diagnosis Criteria.

Clinical	Laboratory
1. Vascular thrombosis: one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ	1. Lupus anticoagulant (LA)
2. Pregnancy morbidity;	2. Anti cardiolipin (aCL)
a) One or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation	3. Anti-β2GPI antibodies
b) One or more premature births of a morphologically normal neonate before the thirty-fourth week of gestation because of eclampsia, severe preeclampsia, or placental insuffciency	
c) Three or more unexplained consecutive spontaneous abortions before the tenth week of gestation	

again and treated with warfarin, prednisolone, and antihypertensive medication. In younger patients, like these 2 patients, it is easier to remind the test for SLE and APS. Our patient was aged 64 years old and the diagnosis of SLE was overlooked in previous hospitalizations, probably because of his age and gender.

In conclusion, prevention of recurrent stroke should be considered as a part of rehabilitation. SLE is one of the important reasons causing recurrent strokes. Ischemic stroke as the first manifestation of the disease is rare and thus the diagnosis of SLE may be overlooked during etiologic investigation of recurrent strokes in emergency or neurology clinics. An early diagnosis in SLE and appropriate anticoagulation medication are vital for patients with stroke. SLE should always be in our mind during etiologic investigation of stroke in order to decrease the risk of recurrence by means of secondary prevention.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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