

## Recurrent Stroke Due to Antiphospholipid Syndrome Remitted by Immunotherapy, Not by Anticoagulation Therapy: A Case Report and Literature Review

Sir,

Antiphospholipid syndrome (APS) is defined by the occurrence of thrombosis with the persistent presence of circulating antiphospholipid antibodies: lupus anticoagulant, anticardiolipin, and/or anti- $\beta$ 2-glycoprotein I (GPI) antibodies.<sup>[1]</sup> Thrombotic events occur in arterial and venous beds. Ischemic strokes and transient ischemic attacks are the most common arterial events.<sup>[1,2]</sup> In young stroke patients <50 years of age, APS is considered as an important etiologic factor.<sup>[1,2]</sup> The management of thrombosis in patients with APS is a subject of controversy.<sup>[1-3]</sup> In the literature, guidelines for the prevention of stroke recommend that anticoagulant therapy is considered for patients who meet the criteria for APS.<sup>[4]</sup> We herein report a patient with APS who presented with recurrent cerebral infarctions despite anticoagulant therapy and remitted by immunotherapy.

A 43-year-old woman visited for left-hand clumsiness. Two years ago, she had taken oral anticoagulation therapy for 2 months due to deep vein thrombosis of the right leg. She

also had antiplatelet medication (aspirin 100 mg/day) for 1 year. She had no history of hypertension, diabetes, or thyroid disease. Neurological examination revealed normal motor functions, except mild weakness of the left hand. Magnetic resonance image (MRI) study of the brain revealed embolic infarctions in multiple vessel territories [Figure 1a] without definite intracranial vessel abnormality. Laboratory tests showed moderate thrombocytopenia ( $85 \times 10^3/\mu\text{L}$ ), elevated D-dimer (319 ng/ml, the normal range of 24–278), and raised lupus anticoagulant antibody level (3.1, the normal range of 0.8–1.2). Both prothrombin time and partial thromboplastin time were normal. Other autoimmune markers such as antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, anti-smooth muscle antibody, cryoglobulin, phospholipid immunoglobulin G (IgG)/IgM antibody, anti-dsDNA antibody, anticardiolipin IgG/IgM antibody, anti-thrombin III, protein C/S level, and fibrinogen were normal. Other biochemical parameters were also within the normal ranges.

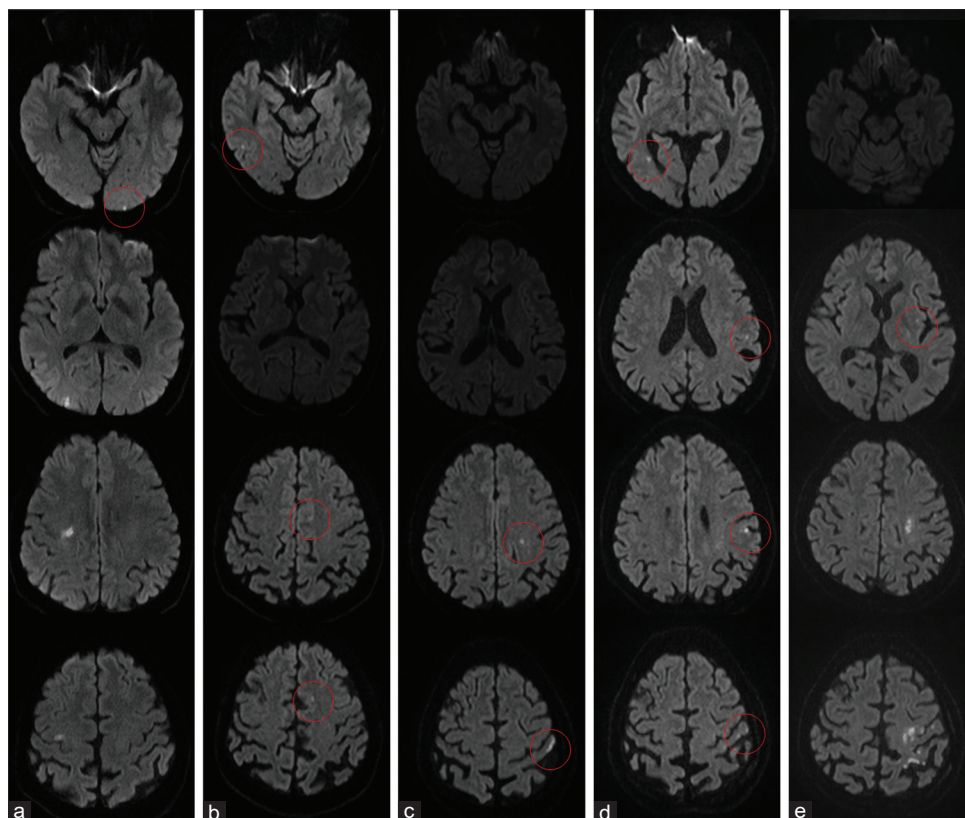
For her left-hand clumsiness, the patient took oral anticoagulation (warfarin) again for 2 months and remained on antiplatelet medication (aspirin 100 mg/day). On follow-up (F/U) day 667, she complained of mild right limb weakness, which began 2 weeks before. F/U MRI revealed new lesions in multiple vessel territories [Figure 1b]. Oral anticoagulation was started again. Prothrombin time with the international normalized ratio (INR) was regularly checked.

On day 861, F/U MRI showed a new small lesion on the left cortico-subcortical region and a history of right finger weakness for 1 week was reported [Figure 1c]. INR level was 1.81. Antiplatelet (aspirin 100 mg/day) medication was added to anticoagulation therapy. On day 1115, the patient was admitted due to new infarction on account of right-hand weakness [Figure 1d]. No vascular abnormality was observed in the magnetic resonance angiography of the brain and neck. INR level was 2.09, and platelet count was 30,000. We stopped anticoagulation to avoid bleeding risks. Anemia (hemoglobin of 8.5 g/dL) was identified for the first time. In addition, ANA, anti-dsDNA antibody, and lupus anticoagulant antibody were positive. During hospitalization, her symptoms deteriorated, and MRI showed new embolic infarction [Figure 1e]. To treat hematologic abnormality and arterial thrombosis, steroid pulse therapy (1000 mg methylprednisolone) was used for 5 days. Platelet count recovered rapidly. The neurologic symptom was also stabilized. Immunotherapy has been changed from steroid to azathioprine (100 mg, 2 mg/kg).

Thirty-two months of F/U, neurologic deterioration did not recur, although INR level did fluctuate  $<2$ . Brain MRI to check asymptomatic change did not show any parenchymal lesion. In several laboratory studies, ANA and lupus anticoagulant antibody remained positive. Other antibodies, ANCA, anti- $\beta$ 2-GPI IgG/IgM, anti-dsDNA, anticardiolipin IgG/IgM, and phospholipid IgG/IgM, were negative.

The occurrence of thrombosis with the persistent presence of circulating antiphospholipid antibodies of at least 12 weeks is necessary for the diagnosis of APS.<sup>[2]</sup> Among antiphospholipid antibodies, lupus anticoagulant is thought to be most strongly related to thrombosis.<sup>[1]</sup> In patients with ischemic stroke who have APS, antiplatelet therapy or anticoagulant therapy may be considered depending on the risks for thrombosis and bleeding.<sup>[3,4]</sup> In patients with definitive APS, venous thrombosis may be prevented with oral anticoagulation to a target INR of 2.0–3.0.<sup>[1]</sup> In contrast, patients with definitive APS presenting with arterial thrombosis are at an increased risk for recurrence, despite oral anticoagulation to a target INR of 2.0–3.0. In such cases, high-intensity anticoagulant therapy to an INR of 3.0–4.0 may be more effective in preventing recurrences.<sup>[1,3]</sup> To date, the role of immunomodulation to prevent thromboembolic events has not been established.<sup>[3,5]</sup>

In our case, ischemic stroke was recurrent despite anticoagulation and antiplatelet medication. Bleeding risk with high-intensity anticoagulation due to thrombocytopenia was not negligible. Immunotherapy recovered thrombocytopenia



**Figure 1:** (a-e) Sequential brain diffusion magnetic resonance image. Tiny lesions are in red circles. Images with no acute lesion are darkened

rapidly and prevented ischemic stroke, even when INR level was not at therapeutic level. Thrombocytopenia is one of the possible clinical features associated with antiphospholipid antibodies.<sup>[6]</sup> Antibodies directed against platelet glycoproteins are relevant to thrombocytopenia in patients with APS.<sup>[6]</sup> Thrombocytopenia is also one of the clinical features and diagnostic criteria of systemic lupus erythematosus (SLE).<sup>[7]</sup> SLE appears to increase the risk of vascular thrombosis in patients with APS. However, such association is not considered strong enough to guide clinical decisions in secondary prevention.<sup>[1]</sup> In the beginning, our patient did not fulfil the diagnostic criteria of SLE (2 of 17 criteria matched for lupus anticoagulant positivity and thrombocytopenia). A diagnosis of SLE was made with ANA antibody positivity and hemolytic anemia (direct Coombs test positivity) during the F/U period.<sup>[7]</sup> Thus, immunotherapy was not considered as first-line treatment. In addition, APS was considered as primary type initially, this diagnosis should be change to secondary APS associated with SLE. With anticoagulation and immunotherapy, thrombotic neurologic symptoms were stabilized, and effective prevention of another thrombosis was established. Immunotherapy could be one of the therapeutic options for arterial recurrent thrombotic events in patients with APS, especially when accompanied by thrombocytopenia. It is also important that laboratory autoimmune markers should be investigated repeatedly with appropriate intervals.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

**Jin-Mo Park, Kyung Yoon Eah**

Department of Neurology, Dongguk University College of Medicine, Dongdae-Ro, Gyeongju 38067, Korea

**Address for correspondence:** Prof. Jin-Mo Park, Department of Neurology, Dongguk University College of Medicine, 87 Dongdae-Ro, Gyeongju 38067, Korea.  
E-mail: neuropjm@gmail.com

### REFERENCES

1. Ruiz-Iratorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, *et al.* Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a task force at the 13<sup>th</sup> International Congress on antiphospholipid antibodies. *Lupus* 2011;20:206-18.
2. Sciascia S, Sanna G, Khamashta MA, Cuadrado MJ, Erkan D, Andreoli L, *et al.* The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: A systematic review. *Ann Rheum Dis* 2015;74:2028-33.
3. Giannakopoulos B, Krilis SA. How I treat the antiphospholipid syndrome. *Blood* 2009;114:2020-30.
4. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, *et al.* Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2160-236.
5. Asherson RA, Baguley E, Pal C, Hughes GR. Antiphospholipid syndrome: Five year follow up. *Ann Rheum Dis* 1991;50:805-10.
6. Galli M, Daldossi M, Barbui T. Anti-glycoprotein Ib/IX and IIb/IIIa antibodies in patients with antiphospholipid antibodies. *Thromb Haemost* 1994;71:571-5.
7. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, *et al.* Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677-86.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

DOI: 10.4103/aian.AIAN\_433\_18