Ann Vasc Dis Vol. 17, No. 4; 2024; pp 409–412

Online October 8, 2024
doi: 10.3400/avd.cr.24-00040

Case Report

Preceding Antiphospholipid Syndrome before the Onset of Systemic Lupus Erythematosus Presenting with Iliocaval Deep Vein Thrombosis: A Case Report and Literature Review

Masaya Nakashima, MD, and Masayoshi Kobayashi, MD

Antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) are similar to be characterized by thromboembolic events and various clinical manifestations. We experienced a 21-year-old man with acute iliocaval deep vein thrombosis (DVT). Primary APS was initially diagnosed on the criteria, and after multidisciplinary treatment, iliocaval DVT was gradually regressed. Six months later, the patient complained of acute enteritis, followed by peripheral neuropathy and butterfly lupus. SLE was diagnosed, which suggested that the onset of SLE was preceded by APS. This case raises the question of a present consensus that these two diseases are clearly different clinical entities, although these are closely related.

Keywords: antiphospholipid syndrome, systemic lupus erythematosus, iliocaval deep venous thrombus

Introduction

Anti-phospholipid syndrome (APS) and systemic lupus erythematosus (SLE) are perceived as two closely related diseases.[1–4] These are similar to be characterized by thromboembolic events and various clinical manifestations, including positive for serum immunological antibodies.[1–4] Inferior vena cava (IVC) thrombosis, deep vein thrombosis (DVT), and other thromboembolic events can similarly occur as complications in APS and SLE. We treated a young man who presented with acute iliocaval venous thrombus and carried antiphospholipid antibodies. Primary APS was diagnosed and treated because he did not suffer from other autoimmune diseases. Six months later, however, the patient suddenly revealed the peripheral symptoms of neuropathy, lupus erythematosus, and enteritis. An increase in SLE clinical and immunological scores was demonstrated in the latter event compared with the initial event, which suggested the onset of SLE was preceded by APS. This report describes an urgent procedure and prognosis of APS/SLE venous thrombus. Herein, we experienced an interesting case with iliocaval thrombus with floating submasssive IVC and lower limb deep vein thrombus in APS young man secondary presenting with SLE.

Case Report

A 21-year-old man was referred to our hospital with a left swollen leg and tenderness that had developed over 1 week. He had been complaining of left leg edema at rest and partial hip pain. He had no pertinent past illness and family history. Routine laboratory tests revealed that white blood cell (WBC) 5900/μl, hemoglobin (Hb) 13.0 g/dl, and platelet (Plt) 120000/μl were all within the normal range. fibrin/fibrinogen degradation products (FDP) 25.9 μl/ml, D dimer 13.2 μl/ml, and activated partial thromboplastin time (APTT) 67 sec were increased. Enhanced computed tomography (CT) venography revealed a continuous filling defect via the IVC to the left popliteal vein and contralateral right popliteal vein (**Fig. 1A**). CT showed no pulmonary thromboembolism; however, repeated blood measurement revealed that anticardiolipin (aCL) antibody was positive, lupus anticoagulant (LAC) was positive, ds-DNA was positive, but anti-nuclear antibody (ANA) was negative, anti-Jo1 was negative, C3, C4 complement fraction and protein C and S were normal. The hematological physician diagnosed him first time with DVT associated with primary APS, which does not meet eligibility for SLE criteria of European League Against Rheumatism/American College of Rheumatology 2019 (**Table 1**).[1,2]

Department of Vascular Surgery, Tokoname Municipal Hospital, Tokoname, Aichi, Japan

Received: April 11, 2024; Accepted: August 20, 2024
Corresponding author: Masaya Nakashima, MD. Department of Vascular Surgery, Tokoname Municipal Hospital, 3-3-3 Asukadai, Tokoname, Aichi 479-8510, Japan
Tel: +81-569-35-3170
E-mail: tkdr-3697@tac-net.ne.jp

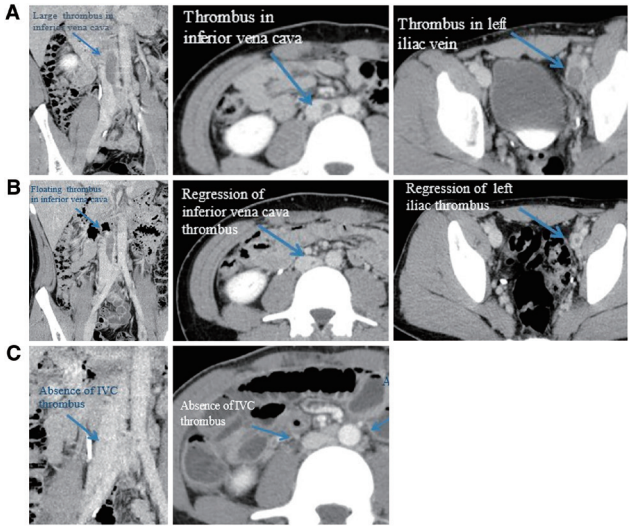

Fig. 1 The change in CT image according to the therapy of thrombosis. (**A**) On the days of APS onset, CT venography showed IVC and left iliac venous thrombus. (**B**) Days 28 after intensive rivaroxaban treatment, CT venography revealed IVC and iliac venous thrombus regression. (**C**) Days 196 after APS onset, CT venography revealed that the IVC thrombus had disappeared completely. APS: antiphospholipid syndrome; CT: computed tomography; IVC: inferior vena cava

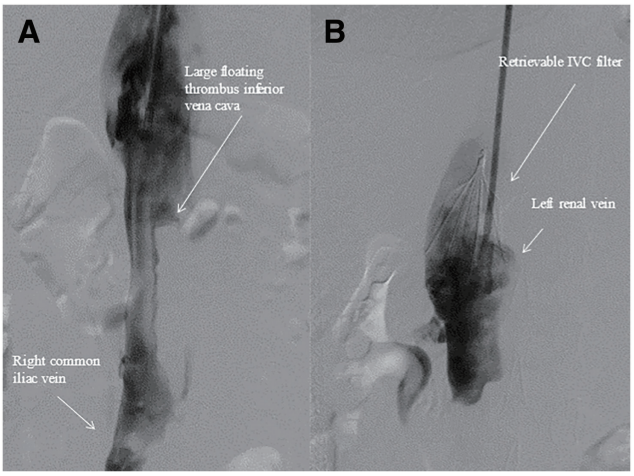

Fig. 2 (**A**) Digital subtraction angiography revealed a filling defect of floating IVC thrombus after intensive oral rivaroxaban. (**B**) Catheter venography showed that the IVC filter (DENALI) was temporarily implanted in the supra-renal vena cava. IVC: inferior vena cava

Table 1 Antiphospholipid assay for the diagnosis of antiphospholipid syndrome and other serological assay and EULAR/ACR 2019 score for the diagnosis of SLE

Diagnosis	Laboratory serologic assay, clinical score		Onset	After 6 months
Antiphospholipid syndrome	Antiphospholipid	Lupus anticoagulant (<1.6)	Positive (2.0)	Positive (2.41)
		Anticardiolipin antibody (<12.3)	Positive (28)	Positive (32)
		Anti-β2-glycoprotein	Negative	Negative
	Other lupus-related autoantibodies	Antinuclear antibody	Negative	Positive
		Anti-Ds-DNA antibody	Negative	Positive
	Other autoantibodies	Anti-Jo1	Negative	Negative
	Compliment	C3 (mg/dL) (86–160)	91	36
		C4 (mg/dL) (17–45)	11	11
	Protein C (%) (70–150)		95	N/A
	Protein S (%) (95–135)		101	N/A
SLE (EULAR/ACR/2019)	SLE clinical score		0	13 (WBC < 4000[3]; Butterfly lupus[5]; and protein urea[4])
	SLE immunological score		2	10
	Total score (the cutoff for classification is 10)		2	23

SLE: systemic lupus erythematosus

The patient hoped outpatient follow-up and intensive direct oral anticoagulation (rivaroxaban, 15 mg twice daily for 21 days, followed by 15 mg once daily) was selected in the choice of treatment[5]. His left leg edema was resolved gradually; however, after 21 days of rivaroxaban treatment, enhanced CT detected the regression of residual IVC, iliofemoral, and popliteal venous thrombus, hence with a floating large thrombus of IVC at 4 weeks after onset (**Fig. 1B**), which required immediate catheter-directed thrombolysis (CDT) and emergency supra-renal temporary IVC filter: Denali (Bard, Covington, Ga, USA) implantation via a right jugular vein to the heritage the risk of the fatal pulmonary thromboembolism (**Fig. 2**). Secondary emergency CDT was performed to distribute the lytic agent after total 120000 U urokinase bolus using a multi-sideport 18G infusion catheter (Smiths Medical, Inc., USA). (A low-dose regimen is administered at

Table 2 Laboratory episode for APS and SLE

Blood cell count, laboratory examination, and coagulation tests	Onset	After 6 months
WBC (/μL)	5900	2400
Hb (g/dL)	12.7	11.3
Plt (/μL)	91000	13300
CRP (mg/dL)	1.05	1.98
CK (IU/L) (59–248)	59	18
LDH (IU/L) (124–222)	222	238
AST (IU/L)	20	20
ALT (IU/L)	17	18
Protein urea	negative	2+
APTT (24–67)	67	68
PT (70–160)	96	92
FDP (μg/dL) (0–4.9)	25.9	42.6
D dimer (μg/dL) (0.1–0.9)	13.2	9.8

APS: antiphospholipid syndrome; APTT: activated partial thromboplastin time; ALT: alanine aminotransferase; AST: aspartate transaminase; LDH: lactate dehydrogenase; CK: creatine kinase; CRP: C-reactive protein; SLE: systemic lupus erythematosus; WBC: white blood cell; Hb: hemoglobin; Plt: platelet; PT: prothrombin time; FDP: fibrin/fibrinogen degradation products

urokinase120000 IU, PG E1 20 μg, and heparin10000 unit/day through 4Fr. sheath via the right femoral retrograde approach.) No secondary additional interventions were required and the patient was discharged from our hospital 2 weeks after thrombolysis. Follow-up CT at 1 month showed regression of IVC and iliofemoral thrombus, and a more complete resolution of the bilateral popliteal venous thrombus.

At 6 months (196 days) after venous thrombus onset, he had a symptom of sudden fever, abdominal pain, and butterfly skin rash on his face to the emergency room. Laboratory tests suggested leukopenia, WBC 2400/μL was decreased and revealed Hb 11.3 g/dL, Plt 110000/μL, C-reactive protein 0.18, FDP 10.1 μL/mL, D dimer 3.2 μL/mL, and APTT67 sec without the normal range, and ds-DNA and ANA were positive (**Table 2**).

Enhanced CT showed small bowel edema and ascites, though the complete resolution of the residual thrombus from IVC to the left iliofemoral vein (**Fig. 1C**).

Furthermore, the peripheral symptoms of the glove and stocking neuropathy were observed on admission, suggesting an active SLE complicated with lupus enteritis, which fulfills the above 10 points of the EULAR/ACR SLE criteria.[1] He was secondarily transferred to the emergency room of a medical university hospital. He was diagnosed with severe active SLE and presented with acute lupus enteritis. He had been treated with corticosteroid, immunosuppressive treatment by cyclophosphamide, and aggressive plasmapheresis. 12-month follow-up CT did not present any recurrence of systemic venous thrombus at the university hospital.

Discussion

SLE and APS are perceived as two closely related diseases.[1–4] These are similar to be characterized by thromboembolic events and various clinical manifestations, including positive for serum immunological antibodies.[1–4] IVC thrombosis, DVT of lower extremities, and other thromboembolic events can similarly occur as a complication in SLE and APS.[1–4] Although patients with primary APS and SLE share lupus susceptibility genes, no report demonstrated that patients with primary APS developed SLE with a definitive diagnosis even after a long follow-up.

APS is characterized by recurrent pregnancy loss with the lupus anticoagulant and the presence of arterial or venous thrombotic events by serious obstetrical complications associated with the persistent presence of antiphospholipid antibodies (aPL).[1] aPL is indeed one of the most common and important acquired biomarkers for thrombosis, which is a collective term for a set of autoantibodies with closely related but different specificity. The presence or absence of SLE modifies the clinical or seroimmunological expression of APS.[1–4,6]

The presence of aPL has been described in about 40%–50% of SLE patients, while about 20%–30% of APS patients are complicated with SLE.[4] It has been shown that SLE with aPL positive (secondary APS) have a higher risk of thrombotic complications than classical primary APS, and a striking increase in the number of thrombotic events was observed.[2] It is extremely important to identify the characteristics of aPL, and "triple positivity": lupus anticoagulant, anticardiolipin antibody, and anti-beta2-GP1 antibody have the strongest prognostic value in terms of thrombotic events and recurrence.[4–6] SLE itself is an independent risk factor for developing both arterial and venous thrombotic events. However, fewer studies in the absence of APS are available for SLE patients presenting with venous thrombosis especially.

SLE mainly affects women in their childbearing years. The diagnosis of SLE is often complex and generally based on clinical and laboratory findings after excluding alternative diagnoses.[4–6] SLE also presents with variable clinical manifestations ranging from mild joint and skin symptoms to life-threatening various systematic involvement; however, thrombotic events are not included in the diagnostic criteria.[4] In this case, after 6 months of SLE onset, CT revealed that the IVC thrombus had disappeared, and after 12 months of follow-up, CT did not present any recurrence of systemic venous thrombus in spite of the need for cyclophosphamide and plasmapheresis. Danowski divided APS and SLE into three groups: primary APS, APS associated with SLE, and SLE patients with aPL.[1] Interestingly, the frequency of thrombosis and pregnancy loss is greater in APS associated with SLE than in primary APS. High triglycerides ($p = 0.001$), hereditary thrombophilia ($p = 0.02$) and, in particular, aPL ($p = 0.04$)

are major associated risk factors of venous thrombus. In SLE with secondary APS, symptomatic arterial and venous thrombotic events were characterized by unresolved pathogenic mechanisms, and ultimately, it is potentially life-threatening when an SLE patient involves a large/massive thrombotic event.[3–6] The occurrence of APS can be associated with SLE, a complex clinical scenario with thromboembolic events and therapeutic complications, and the most important risk factor is lupus activity and the presence of aPL.[1–4]

Approximately 70% of SLE patients follow a relapsing-remitting course, which can occasionally include an initial period of high-intensive therapy for organ and life-threatening SLE.[3,4,6] In severe active SLE, such as lupus nephritis, neuropathy, and enteritis, the treatment is dependent on the severity of the inflammation and/or thrombosis. The patient should be treated accordingly with immunosuppression and/or anticoagulation.[7,8] In this case, SLE activity was aggravated, but systemic venous thrombus was resolving, and there was no association between APS/SLE activity and thrombotic exacerbation.[1,8,9] Even if primary APS were diagnosed, it was necessary to pay attention to the onset of SLE. It is noteworthy that no other complications influencing vascular patency have occurred so far after this treatment.[9] Carefully considering what is known about thrombotic events of APS and/or SLE patients in the acute stage will provide clues to unraveling the complexity of SLE-related mechanisms is linked so frequently; however, this case raises an undoubted question for a present consensus that these two diseases are a clearly different clinical entity and severity although these are close related. Although it is not possible to check the several seroimmunological examinations when the prognosis for primary APS, even if accidental APS was diagnosed, it was necessary to pay attention to on set the secondary SLE; here we described a clinical thrombotic course of primary APS and secondary SLE with closely related but different specificity.

Conclusion

APS and SLE are clearly different clinical entities, and there was no association between APS/SLE activity and thromboembolic exacerbation. This case raises the question of a present consensus that these two diseases are clearly different clinical entities, although these are closely related. The multidisciplinary treatment for systemic thrombosis of APS/SLE should be determined on a case-by-case basis with careful follow-up.

Declarations

Acknowledgments

The authors thank Dr. Yoshio Takesue for his kind support during the preparation of this article.

Ethical approval

Informed consent has been obtained from both patients for the publication of this case report and accompanying images. In this article, each author has no financial conflict. This article was approved by the Ethical Committee of Tokoname Municipal Hospital (Permission number: 2024-02).

Funding

The author(s) received no financial support for this article's research, authorship, and/or publication.

Disclosure statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

Study conception: MN
Data collection: MN
Analysis: MN
Investigation: MN
Critical review and revision: All authors
Final approval of the article: All authors
Accountability for all aspects of the work: All authors.

References

1) Danowski A, De Azevedo MNL, de Souza Papi JA, et al. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. J Rheumatol 2009; **36**: 1195–9.
2) Uthman I, Noureldine MHA, Ruiz-Irastorza G, et al. Management of antiphospholipid syndrome. Ann Rheum Dis 2019; **78**: 155–61.
3) Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. N Engl J Med 2018; **378**: 2010–21.
4) Bazzan M, Vaccarino A, Marletto F. Systemic lupus erythematosus and thrombosis. Thromb J 2015; **13**: 16.
5) de Groot PG, de Laat B. Mechanisms of thrombosis in systemic lupus erythematosus and antiphospholipid syndrome. Best Pract Res Clin Rheumatol 2017; **31**: 334–41.
6) Fanouriakis A, Tziolos N, Bertsias G, et al. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis 2021; **80**: 14–25.
7) Pons-Estel GJ, Andreoli L, Scanzi F, et al. The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimmun 2017; **76**: 10–20.
8) Arora S, Nair S, Prabhu R, et al. Role of direct oral anticoagulation agents as thromboprophylaxis in antiphospholipid syndrome. Cureus 2021; **13**: e19009.
9) Otsuka R, Saito S, Yamamoto T, et al. Recurrent mural thrombosis of the ascending aorta in a patient with antiphospholipid syndrome. Ann Vasc Dis 2022; **15**: 77–80.