

[CASE REPORT]

Reversible Parkinsonism and Multiple Cerebral Infarctions after Pulmonary Endarterectomy in a Patient with Antiphospholipid Syndrome

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Abstract:

Antiphospholipid syndrome (APS) is a cause of chronic thromboembolic pulmonary hypertension (CTEPH) and it is associated with an increased risk of postoperative neurological complications. We experienced a case of reversible parkinsonism after pulmonary endarterectomy (PEA) and subsequent multiple cerebral infarctions under standard anticoagulation therapy in a patient with CTEPH associated with APS. Strict management using a combination of antiplatelet and anticoagulation therapy should be considered in patients with a high titer of triple antiphospholipid antibodies in the perioperative period. We should be aware of the high risk of postoperative neurologic manifestations in patients with APS.

Key words: perioperative management, hypoxic ischemic encephalopathy, antiphospholipid antibody, chronic thromboembolic pulmonary hypertension, antiplatelet therapy, anticoagulation therapy

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by venous or arterial thrombotic complications with persistent antiphospholipid antibodies. APS increases the risk of chronic thromboembolic pulmonary hypertension (CTEPH), for which pulmonary endarterectomy (PEA) is a treatment of choice (1). PEA is a surgical procedure performed under total cardiopulmonary bypass and deep hypothermic circulatory arrest. The prevention of cerebrovascular disturbances during PEA is an important issue. In addition, APS is associated with an increased risk of postoperative neurological complications (2).

We herein report a case of diversified neurological complications after PEA in a patient with CTEPH associated with APS.

Case Report

A 34-year-old man was admitted because of progressive dyspnea over the previous 11 months [World Health Organization (WHO) functional class III]. He had a significant 10-year medical history of APS, which was diagnosed based on subclavian arterial thrombosis and the presence of antiphospholipid antibodies. Systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody (ANCA)-related arteritis, and other connective tissue diseases were ruled out as the etiology for the subclavian lesion by his autoantibody profile. He had been prescribed antiplatelet aspirin and anticoagulant warfarin.

On admission, a clinical evaluation revealed absent pulsations of the right upper and right lower limbs. Laboratory results were as follows: platelets 71,000/ μ L; C-reactive pro-

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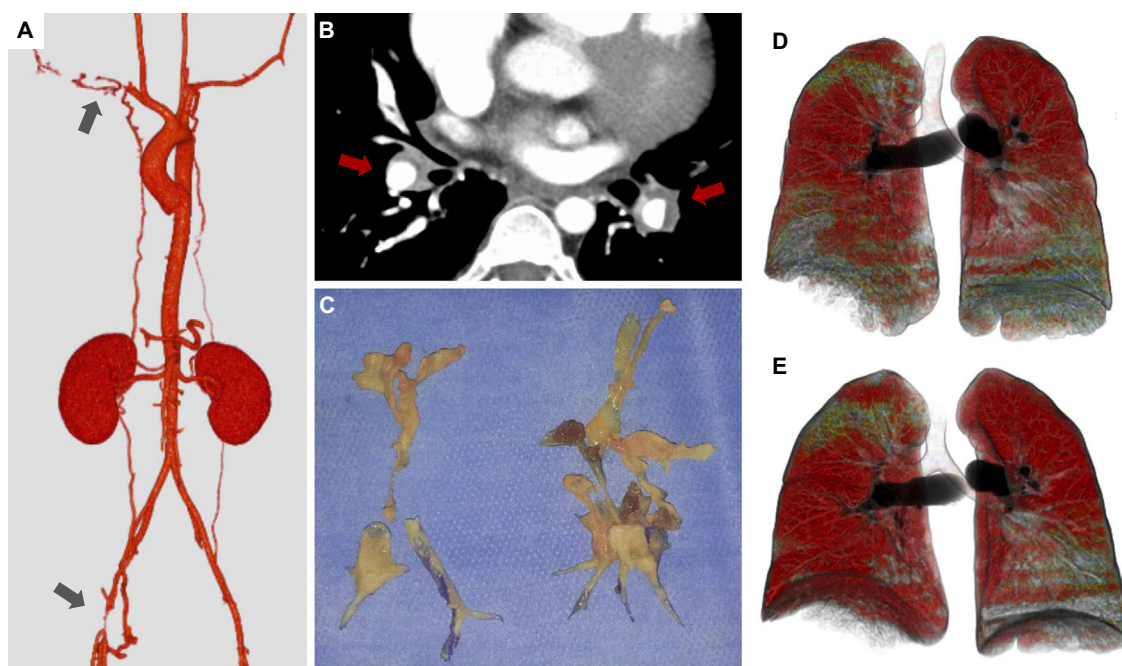


Figure 1. Clinical images of CTEPH associated with APS. CT angiogram of the aorta (A) showing occlusion of the right subclavian artery and narrowing of the right common femoral artery (arrows). Chest enhanced CT (B) showing defects of contrast in the central pulmonary arteries without stenosis, suggesting thrombosis (arrows). Surgical specimen (C) from bilateral pulmonary endarterectomy. Dual energy enhanced chest CT before (D) and after (E) pulmonary endarterectomy. CTEPH: chronic thromboembolic pulmonary hypertension, APS: antiphospholipid syndrome

tein (CRP) 0.56 mg/dL; and serum brain natriuretic peptide (BNP) 67.4 pg/mL. He had a prolonged activated partial thromboplastin time (APTT) (75.6 s, normal range: 26.0–38.0 s) and elevated D-dimer (1.2 $\mu\text{g/mL}$). Beta 2-glycoprotein I dependent anticardiolipin antibody ($\beta\text{2GP I}$: 101 U/mL), anticardiolipin antibody (aCL: 83 U/mL), and lupus anticoagulant (LAC: 2.5 IU) production were elevated. Echocardiography detected a 45 mmHg tricuspid regurgitation pressure gradient (TRPG) and a compressed left ventricular forming a D-shape. Computed tomography (CT) angiogram of the aorta and its branches showed occlusion of the right subclavian artery and narrowing of the right common femoral artery (Fig. 1A). Enhanced CT identified defects in the bilateral pulmonary arteries (Fig. 1B) and no deep vein thrombosis. Although the differential diagnosis between Takayasu's arteritis (TA) and APS is difficult (3), positron emission tomography (PET) showed no ^{18}F -fluoro-2-deoxy-D-glucose accumulation in the wall of the artery. We therefore diagnosed him with primary APS without TA. Ventilation perfusion lung scintigraphy showed mismatches in the bilateral lower lobes. Right heart catheterization (RHC) revealed an increased mean pulmonary arterial pressure (mPAP: 47 mmHg) with a normal pulmonary capillary wedge pressure (PCWP: 13 mmHg) and elevated pulmonary vascular resistance (PVR: 538 $\text{dyn}\cdot\text{sec}/\text{cm}^5$). After the anatomical distribution of intimal thickening and thromboembolic lesions were reviewed by cardiologists and experienced cardiovascular surgeons, the patient was deemed operable. Three months later, bilateral PEA was performed under

total cardiopulmonary bypass. The total operation duration was 422 minutes, and the duration of total circulatory arrest was 81 minutes. An endarterectomy specimen showed multiple organized thrombi obstructing the pulmonary arteries, suggestive of CTEPH (Fig. 1C).

On postoperative day 1, the patient was weaned off mechanical ventilation, but presented with akinesia, bradyphrenia, and rigidity in the upper extremities without a resting tremor. On a neurological examination, the muscle tone of all extremities had increased, and the deep tendon reflexes were both normal and symmetrical. T2-weighted fluid-attenuated inversion recovery (FLAIR) brain magnetic resonance imaging (MRI) showed a high-intensity signal in the bilateral basal ganglia (Fig. 2C). Electroencephalogram findings were normal. Laboratory tests showed no evidence of central nervous lupus or other metabolic brain disorders such as metal deposition encephalopathy and hepatic encephalopathy. Based on the neurologic assessment, the patient was diagnosed with Parkinsonism.

The patient was treated with heparin (300 U/h) and warfarin (4.5 mg/day) after PEA, but the activated partial thromboplastin time (APTT) and international normalized ratio of prothrombin time (PT-INR) were not prolonged compared to before PEA (Fig. 3A). We suspected that the hypoxic ischemic encephalopathy (HIE) from the operation and the pathologic condition of poor prophylaxis induced cerebral microembolism and decreased the cerebral circulation. Due to a poor dietary intake, we replaced heparin and warfarin with edoxaban on day 18, after which his neuro-

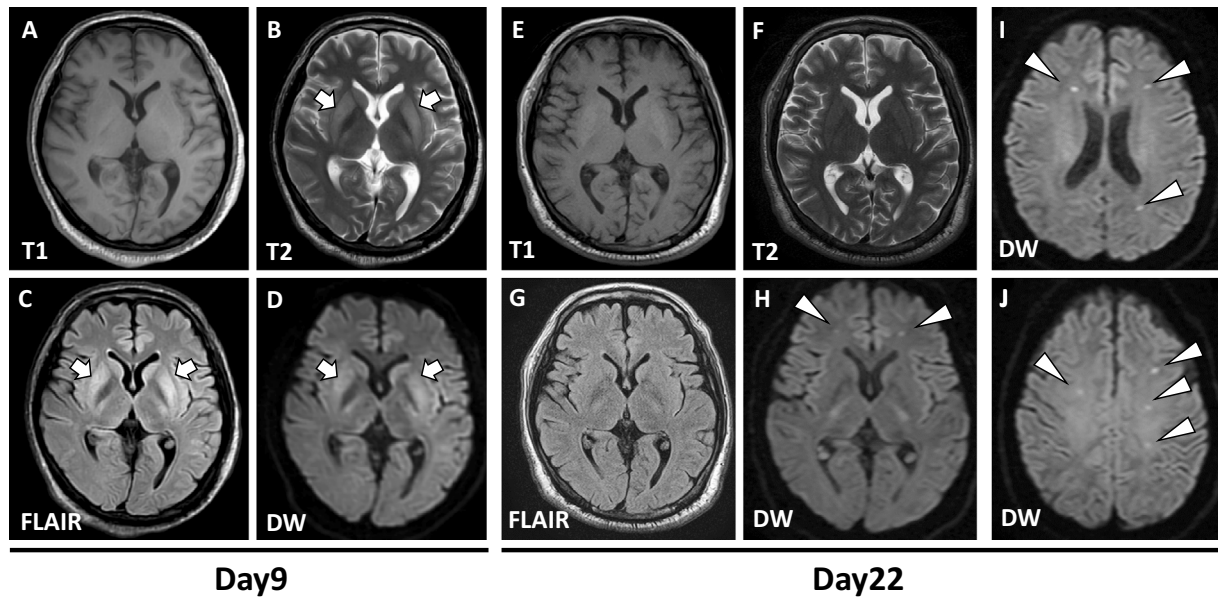


Figure 2. MRI images of the case. Although T1 brain MRI (A, E) findings were normal, T2 (B), FLAIR (C), and DW (D) brain MRI showed a high-intensity signal in the bilateral basal ganglia on day 9 (arrows) that returned to normal on day 22 (F, G, H). DW brain MRI (H, I, J) showed multiple cerebral infarctions in the bilateral anterior and middle cerebral arteries and left posterior cerebral artery (arrowheads). FLAIR: T2-weighted fluid-attenuated inversion recovery, DW: diffusion-weighted

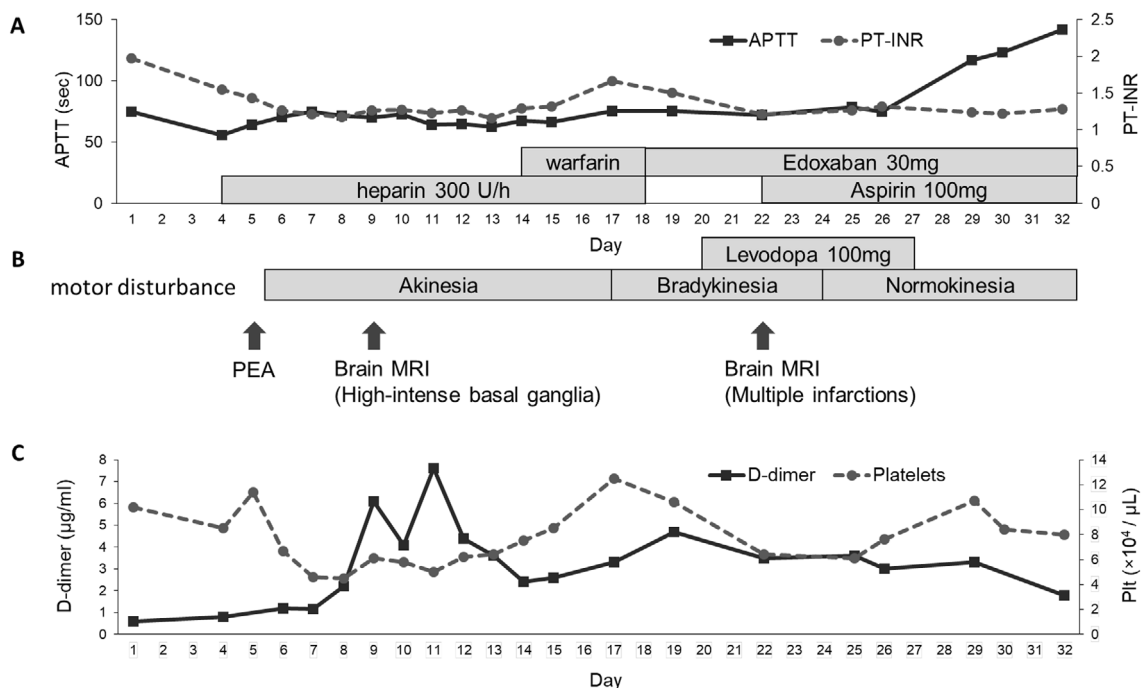


Figure 3. Clinical course with laboratory data and treatments. Despite heparin therapy (300 U/h) (A), the patient presented with transient motor disturbance after PEA, which was confirmed by brain MRI on day 9 (B). Warfarin from day 14 was replaced with edoxaban due to poor dietary intake on day 18. Fluctuations in the D-dimer and platelet levels were observed during the poor anti-coagulation therapy (C). After the detection of newly diagnosed multiple cerebral infarctions at day 22, aspirin was initiated (A). PEA: pulmonary endarterectomy

logical status improved gradually. Next, we tried levodopa therapy for further improvement of his symptoms on day 20. Levodopa was effective, and the high-intensity signal in T2, FLAIR, and diffusion-weighted image (DWI) MRI at the bi-

lateral basal ganglia (Fig. 2B–D) returned to the baseline level on day 22 (Fig. 2F–H). However, diffusion-weighted brain MRI incidentally detected multiple cerebral infarctions in three territories of the bilateral middle cerebral arteries and left posterior cerebral artery (Fig. 2H, I and J). Fortunately, his neurological status improved markedly without any new focal deterioration. We added aspirin on day 22 for the prevention of and stopped levodopa on day 27 (Fig. 3A and B). The results of postoperative examinations were as follows; PAP 22 mmHg; PCWP 10 mmHg; PVR 210 dyn·sec/cm⁵; TRPG 9 mmHg; and BNP 20.8 pg/mL. These findings proved that the operation was successful. Dual energy enhanced chest CT identified a remarkable increase in pulmonary perfusion of the right lower lobe (Fig. 1D and E). He was discharged with mild exertional dyspnea (WHO functional class II) and followed for eight months in our out-patient clinic without deterioration of symptoms.

Discussion

Postoperative neurological complications in APS

We herein report a case of multiple neurological complications, including Parkinsonism and cerebral infarctions, after PEA for CTEPH associated with APS. Fortunately, the Parkinsonism was reversible, and the symptoms of the cerebral infarctions were mild. A higher prevalence of neurological complications after PEA (32–47%) was reported in patients with APS than in those without APS (2, 4). We should recognize the potential postoperative risk of thrombotic events and manage them with optimal antithrombotic care for patients with APS.

Hypoxic ischemic encephalopathy underlying APS presented as transient Parkinsonism

The brain MRI findings of a symmetrical high-intensity signal in the bilateral basal ganglia suggested hypoxic ischemic encephalopathy (HIE) caused by intermittent circulatory arrest during PEA. Notably, the findings of sequential brain MRI were compatible with the clinical findings of akinesia and bradykinesia. The symptoms of Parkinsonism were completely relieved even though levodopa was stopped. D'Armini et al. reported that a high titer of antiphospholipid antibodies correlated with the frequency of transient neurological complications (chorea, delirium, cognition defects) following PEA (4). Furthermore, Milanoy et al. reported that patients with APS presenting with dystonia-Parkinsonism showed a similar high-intensity signal in the bilateral basal ganglia detected by T2-weighted brain MRI (5). Although previous cases have not documented Parkinsonism presenting after PEA, HIE presenting with a transient Parkinsonism phenotype should be noted as a potential neurological manifestation.

The duration of circulatory arrest in this case was relatively long (81 minutes) compared with previous reports

[35 (6)–58 (7) minutes]. However, no paper has previously reported a positive relationship between the frequency of neurological complication and the duration of circulatory arrest. Furthermore, we experienced no cases of HIE aside from the present case among 47 consecutive PEA cases in our institution (circulatory arrest: average 50.4 minutes, range 11–102 minutes). We therefore believe that the Parkinsonism was related to APS. Although the precise mechanism underlying HIE after PEA in patients with APS has yet to be elucidated, it is hypothesized to be an immune-mediated disorder demonstrating the direct binding of antibodies to cells in the nervous systems in APS beyond the classic thrombotic pathway (8). In cases of persistent neurological symptoms despite intensive anticoagulation therapy, the use of steroids might be justified (8).

Multiple cerebral infarctions

Cerebral infarction is the most common arterial thrombotic event in patients with APS (9). Cerebral infarctions were detected by MRI on day 22 in our present patient. Multiple and asymmetrical distributions of the lesions suggested that the embolisms originated from an intra-cardiac or *in situ* thrombosis. We treated the patient with continuous intravenous infusion of heparin and oral warfarin, but neither the APTT nor PT-INR was prolonged compared to before PEA. Surgery, infection, trauma, and thrombocytopenia are known thrombotic risks in APS (10, 11). Indeed, Hisada et al. reported that a decreased platelet count in the patients with APS correlated well with thrombotic events (11), as was observed in our case (Fig. 3). The fluctuating clinical course of D-dimer and platelet levels suggested the occurrence of hypercoagulability after PEA. This suggests the importance of increasing the heparin dose and restarting antiplatelet therapy as soon as possible after PEA. In addition, heparin should be used as a bridge from warfarin before PEA. Only one randomized study thus far has encouraged the combination of antiplatelet and anticoagulation therapy rather than single antiplatelet therapy for secondary prevention in stroke patients with APS (12). The cerebral arterial thrombosis event that occurred under anticoagulation therapy in our case strongly suggests the need for stronger prophylaxis with combined antiplatelet and anticoagulation drugs (13).

Postoperative monitoring

Therapeutic monitoring for thrombophilia is an issue in high-risk patients. Antiphospholipid antibodies affect APTT, making it difficult to monitor the coagulation status in patients administered heparin. Furthermore, we replaced warfarin with edoxaban because of poor dietary intake. The protocol for appropriate monitoring of heparin and direct oral anticoagulants (DOACs) in patients with APS has not yet been established (14). From the present case, we learned that both elevated D-dimer levels and decreased platelet counts should be recognized as potential markers for monitoring these thrombus-related neurological events. Further-

more, direct measurement of the heparin concentration (2.5-3.5 mg/kg) (10) or Xa activity (0.5-1.1 U/mL) (15) may be considered as an appropriate means of monitoring in APS patients.

Conclusion

For APS patients at a high risk of perioperative thrombosis events, early resumption of prophylaxis with the dual combination of anticoagulant and antiplatelet agents might be suitable with appropriate therapeutic monitoring for the optimized management of postoperative neurological complications.

Author's disclosure of potential Conflicts of Interest (COI).

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