Clinical Case Report

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Lower limb vein thrombosis-induced pulmonary embolism and paradoxical multiple arterial embolisms

A case report with a 10-year follow-up

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Abstract

Introduction: Paradoxical embolism (PDE) refers to direct passage of venous thrombi into the arterial circulation through an arteriovenous shunt. It is well-known that the pulmonary thromboembolism (PTE) can cause opening of the foramen ovale leading to paradoxical arterial embolism. Long term follow up of PDE patient over 10 years was not reported in the literature.

Patient concerns: A 57-year-old woman presented with initial symptoms of numbness/weakness and hypoxemia. Ultrasonography and pulmonary arteriography indicated pulmonary thromboembolism.

Diagnosis: Pulmonary embolism and paradoxical multiple arterial embolism or acute PTE concomitant with paradoxical multiple arterial embolism.

Interventions: Craniectomy and anticoagulation treatment was administered and the patient received low-dose warfarin therapy for 10 years.

Outcomes: The patient is currently stable with no abnormalities seen in the deep veins of the bilateral lower limbs. The international normalized ratio (INR) was controlled within the range of 1.20 to 1.51. As this is a 10-year follow-up case report, the patient has responded well to the treatment and has been followed-up. The follow-up has been annual and the patient has been stable

Conclusion: Low intensity and persistent anticoagulation therapy can inhibit blood thrombophilia and reduce the risk of bleeding. It is noteworthy that such an approach used effectively in this patient. To best our knowledge, it is first report for long term follow up PDE patient successfully over 10 years.

Keywords: paradoxical embolism, patent foramen ovale, pulmonary thromboembolism

1. Introduction

Paradoxical embolism (PDE) is regarded as a systemic arterial embolism that requires passage of a venous thrombus into the arterial circulatory system through a right-to-left shunt. It is an unusual condition accounting for nearly 2% of systemic arterial emboli. The patent foramen ovale- (PFO) induced cerebral infarction is relatively rare.[1]

The PFO normally determines a small amount of left-to-right shunt without any significant hemodynamic changes. Nonetheless, in case of increased right atrial pressure, an inversion of the shunt from right-to-left can occur, leading to PDE. Pulmonary thromboembolism (PTE) can induce elevation of right atrial pressure, leading to the opening of the foramen ovale, making the right-to-left shunt possible and providing a motive force for the emboli on the right side of the heart and the venous system to enter the arterial circulation, namely, PDE.[2–4] We report a case of PDE induced by PTE, where continuous anticoagulation treatment was administered with a 10-year follow-up.

2. Case report

A 57-year-old woman, presented in the emergency department with weakness of her both upper and lower left limbs for over 40 days, as well as numbness, weakness and coldness of the right upper limb for 3 days. Her parents died of cerebral stroke and cancer. One elder brother died of hypertensive cardiac infarction. She denied any history of taking contraceptive drugs. On December 23, 2008, the patient experienced weakness of the left limb without an apparent cause. Computer tomography (CT) of the head revealed a large area of infarction in the middle-sized arterial distribution area of the right brain. On the 4th day after initial presentation, she underwent a decompressive craniectomy (Fig. 1A). On the 38th day after initial presentation, the patient had projectile vomiting and complained of numbness

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Informed written consent was obtained from the patient for publication of this case report and the accompanying images.

The authors declare that there are no conflicts of interest in this work.

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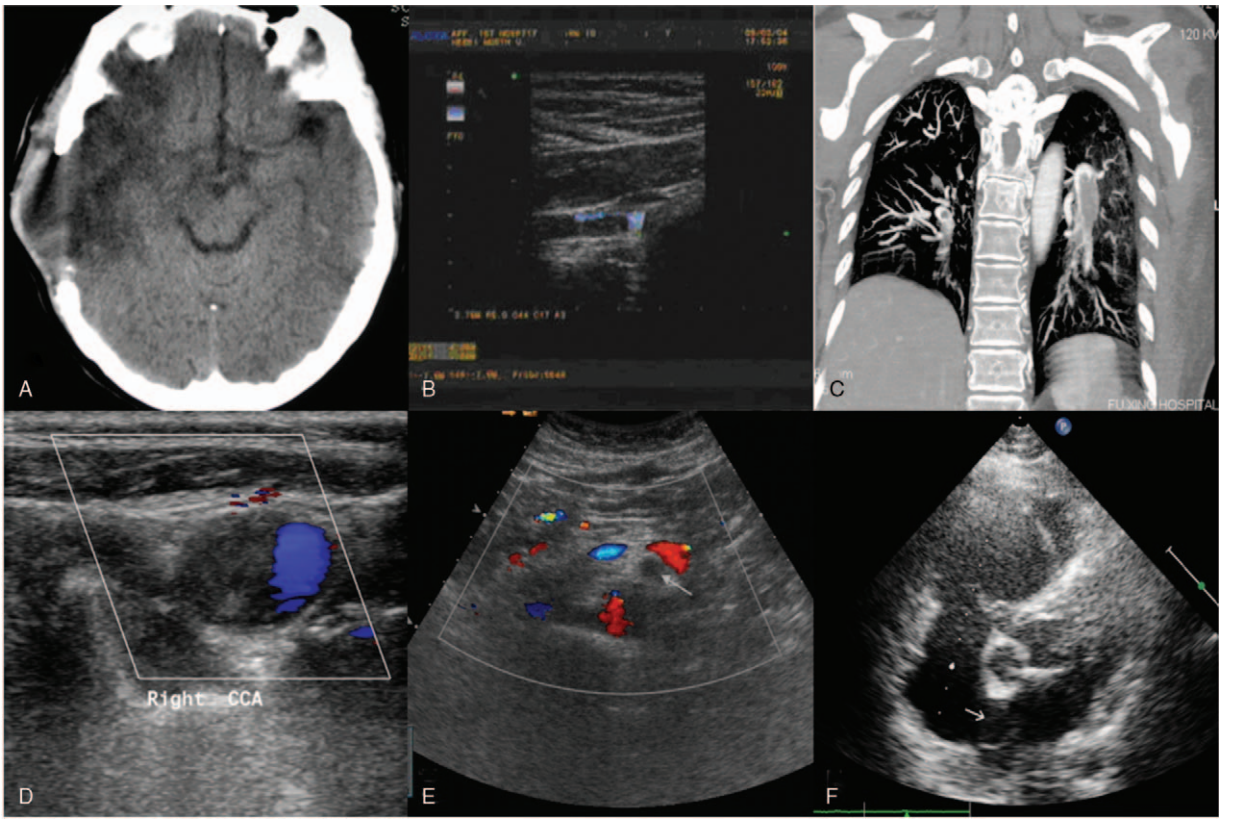

Figure 1. Imaging examinations. Cranial computed tomography (CT) indicated changes after the right temporal decompressive craniectomy (A). Vascular ultrasound revealed solid low echoes at the distal end of the right subclavian artery (B). computed tomography pulmonary arteriography (CTPA) showed wide embolism at the distal end of the bilateral main pulmonary arteries (C). A vascular ultrasound of the neck revealed solid low echoes at the right internal carotid artery (D). The mesenteric arteriovenous ultrasound showed that, the sonolucency of the main trunk and partial branches was poor with no blood flow filling (as indicated by the arrows) (E). Echocardiography indicated the color trans-septal blood flow signals were explored at the oval foramen (as indicated by the arrows) (F).

in the right upper limb with palpitation and decreased skin temperature of the right hand. On the 41st day after initial presentation, the patient's right radial arterial pulsation disappeared. An ultrasound examination showed the presence of multiple embolism at the proximal end of the subclavian artery, the axillary artery, and the proximal end of the brachial artery (Fig. 1B). On the 42nd day after initial presentation, she was admitted to our hospital. Physical examination revealed that the pulsation of the right upper limb artery disappeared, although her bilateral dorsalis pedis arteries had good pulsation. On the second day after hospital admission, the patient complained of numbness in the right leg and foot. Blood gas analysis revealed that partial pressures of oxygen and carbon dioxide were 51.1 mmHg and 25.6 mmHg, respectively. CT pulmonary arteriography (CTPA) indicated a wide pulmonary embolism (Fig. 1C). The carotid arterial ultrasound visualized solid low echoes in the right common carotid artery, and an embolism was also seen in the internal carotid artery (Fig. 1D). Ultrasonography found that the lumens from the distal end of the bilateral popliteal arteries to the posterior tibial arteries had widened, sonolucency was poor, the interiors were filled with hypoechoic echogenic masses, the texture was light and floatation was visible. The lumen of the right popliteal vein was dilated locally, abnormally low-grade solid echoes could be explored in the cavity of the right popliteal vein. The activity of the venous valve had disappeared, and abnormal low- or middle-grade solid echoes could be explored in the cavity of the left popliteal vein. On the 4th day after the admission, the patient complained of abdominal pain and vomiting, and the abdominal vascular ultrasonography indicated the presence of occlusion in the superior mesenteric arteries and branches (Fig. 1E). The pulmonary CT with contrast indicated that a dilated azygos vein shadow was seen on the right side of the large tracheal bifurcation beside the right mediastinum, with a width of about 1.8 cm. The aortopulmonary artery had thickened by about 3.4 cm, the ascending aortal arch at the same level was about 3.2 cm wide, and the cardiac shadows became enlarged with the foremost manifestation of the enlargement in the right heart. Strip-shaped filling defects were seen inside the axillary arterial lumens beyond the right subclavian artery. The echocardiogram indicated that pulmonary artery hypertension was 67 mmHg. The right side of the heart was dilated and color trans-septal blood flow signals could be explored at the oval foramen (Fig. 1F). Warfarin was administered and INR was controlled at about 2.0. After one month, the patient's clinical symptoms improved.

On May 1st, 2009, warfarin was discontinued by the patient. She experienced bilateral lower limb edema after 20 days. The vascular ultrasound showed that the color flow-filling defects of the bilateral popliteal veins were aggravated when compared to

Table 1

Thrombophilia examination.

	26-Mar-2009	21-Oct-2010	19-Mar-2018	reference range
Antithrombase III(%)	109	95	98	89–130
APC-R (s)	135.5	No check	120.6	114–195
Protein C (%)	56	56	64	70–140
Protein S (%)	28	21	56	76–135
Lupus anticoagulant(s)	41.1	36.6	25.5	27–41
VIII factor inhibitor	0.0	No check	No check	<0.6
vWF-Ag	201%	No check	No check	60–150
VIII factor activity C	No check	102	No check	50–150
Anticardiolipin antibody	No check	Negative	Negative	

APC-R = Activated protein C resistance, vWF-Ag = Vascular willebrand factor.

earlier ultrasound examinations, the vessel lumens could not be shriveled completely. Blood analysis showed 1.15 INR, 6.9 mg/L C-reactive protein (CRP) and 250 μg/L D-dimer. The patient was given warfarin, one week thereafter, and the edema of bilateral lower limbs was relieved. A blood thrombophilia-related test revealed protein C and protein S had decreased by 56% and 28%, respectively (Table 1). Subsequently, the patient had a 10-year follow-up and INR was monitored and controlled within the range of 1.20 to 1.51 and warfarin therapy was continued for 10 years. In March 2018, the heart and vascular ultrasound examination indicated that no abnormality was observed in the inner diameter of the atrioventricular septa and all the chambers as well as the shape, structure and movement of all valves. Punctate hyperechoic plaques were formed in the anterior and posterior walls at the right carotid enlargement, an iso-echoic substance filling was seen in the internal carotid arterial lumens, and the vessels had incomplete occlusion. Scattered punctate hyperechoic plaques were formed at the internal walls of the bilateral superficial femoral arteries and the deep arteries below them. However, no abnormalities were observed in the deep veins of the 2 lower limbs.

3. Discussion

Cohnheim (1877) first described PDE as the passage of embolic material through a right-to-left intracardiac shunt into the systemic circulation.[5] It is a relatively rare phenomenon, representing only about 2% of all cases of arterial embolism. However, PDE is often associated with the diagnosis of PFO, estimated to be about 27% to 35% of the normal population.[6,7]

PFO means that the primary and secondary septa cannot normally and naturally fuse after birth. As per normal status, there is no right-to-left shunt (Fig. 2A) However, in cases where right atrial pressure is higher than the left, the thin primary septum is pushed away, and the right-to-left shunt occurs.[8] An elevation in right atrial pressure induces the foramen ovale open; in case of PTE, the sharp increase in the pulmonary arterial pressure induces rapid increase in the right cardiac pressure. The decrease in pulmonary blood flow volume leads to decrease in the left cardiac returned blood volume and an obvious decrease in the left atrial pressure. In case of an obvious increase in the right atrial pressure, the closed foramen ovale is re-opened, and the atrial right-to-left shunt occurs. The vena cava system emboli enter the left cardiac system through the foramen ovale (Fig. 2B).[9–11] Our patient developed the disease acutely due to cerebral infarction. Subsequently, the patient experienced generalized multiple arterial embolisms. the right upper limb arterial embolism induced the symptoms of numbness, pain and decreased skin temperature, and the mesenteric arterial embolism induced the symptoms of abdominal pain and vomiting. Physical examination found the shortness of breath, tachycardia, and pulmonary rales or rhonchi. The blood gas analysis found relatively serious hypoxemia and hypocapnia. The ultrasound examinations indicated damages in pulmonary functions and multiple arterial thrombi. An echocardiogram verified the presence of an obvious right-to-left shunt at the atrial level, and in the meantime the peripheral vascular ultrasonography found that subacute thrombi were visible in the both lower limb venous system. Based on these findings,

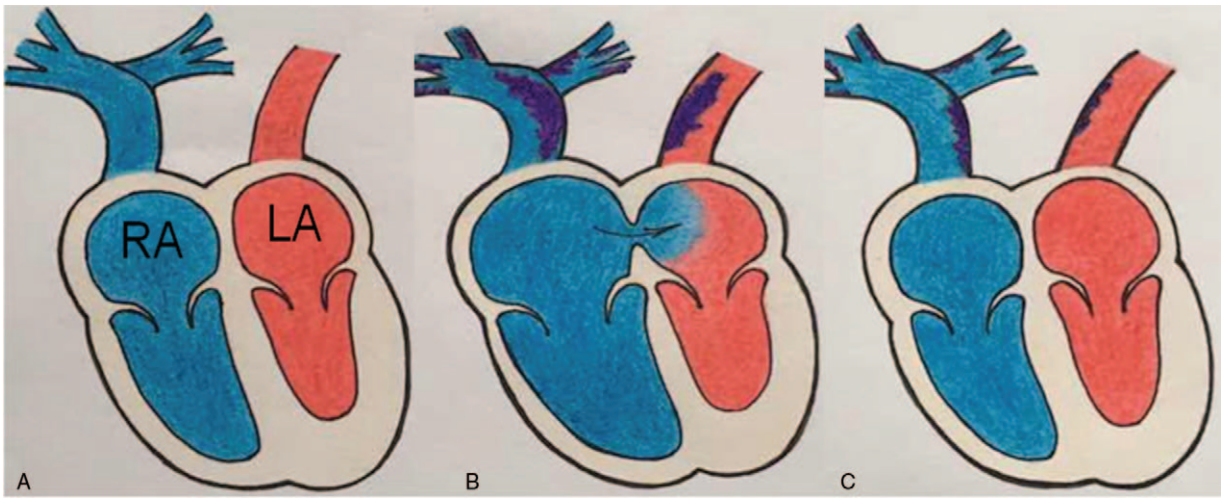

Figure 2. A schematic diagram of a foramen ovale opening and closing. In a normal heart, the foramen ovale closes, separating the right atrium (RA) and the left atrium (LA) (A). p ulmonary thromboembolism (PTE) induces an increase in pulmonary arterial pressure and also right cardiac pressure, leading to an enlargement of the right side of the heart and the opening of the foramen ovale, venous blood leaks from the right atrium through the left atrium into the body (B). After anticoagulant therapy, the patient's pulmonary arterial pressure returned to normal, transesophageal ultrasonic examination found that the foramen ovale had been closed (C).

the diagnosis of acute PTE concomitant paradoxical multiple arterial embolism was made. Pulmonary thromboembolism with PFO can often be complicated by PDE. The acute elevation of pulmonary artery pressure can promote an inversion shunting across the patent foramen ovale, leading to arterial embolism.[12] The blood examinations indicated that blood proteins C and S were lower than normal. Therefore, thrombophilia was also considered.

After a month of persistent and effective anticoagulant therapy, the patient's pulmonary embolism dissolved, which effectively reduced right cardiac pressure and subsequently induced maximal retraction and closure of the foramen ovale propped up by the pressure. A repeat echocardiogram showed shrinkage of the inner diameter of the right side of the heart and decreased pulmonary artery pressure. A transesophageal ultrasound examination found that the foramen ovale was closed (Fig. 2C). The repeat vascular ultrasound showed partial thrombosis organization in the left popliteal vein, tibial-fibular and the right posterior tibial veins.

It is reported in several cases that PDE may complicate pulmonary embolism.[13,14] One study suggested that it is estimated that 70% of these PDE cases are connected with pulmonary embolism. Yet, multiple organ embolic involvement is less common. In the same study, 23% of cases portrayed 2 different embolic sites and only 10% had 3 different sites. Common sites for PDE are the inferior limbs (49%), brain (37%) and, more infrequently, coronary, renal or splanchnic arteries (4.5%).[15]

In order to prevent recurrent arterial emboli or PDE, recommended treatments include mainly systemic anticoagulation and closure of the PFO. The different therapeutic options are not predictors of recurrence as stated in many clinical cases.[16] The duration of anticoagulation therapy might be variable for the thrombotic risk, for instance in patients with moderate risk for venous thrombosis, it should be prescribed for a period of 6 to 12 months. Patients at high risk for venous thrombosis require lifelong anticoagulant therapy.

In this case, 10-year continuous warfarin therapy was used to maintain the patient's INR between 1.20 to 1.51 and the thrombus did not recur. We considered that this kind of low-intensity anticoagulation therapy is effective for patients who lack proteins C and S. Low intensity, persistent, anticoagulation therapy can inhibit blood thrombophilia and reduce the risk of bleeding. It is noteworthy that such an approach used effectively in this patient. To our knowledge, it is first report for long term follow up PDE patient successfully over 10 years.

Author contributions

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