Case Report

Paradoxical Cerebral Embolism as Initial Manifestation of Chronic Thromboembolic Pulmonary Hypertension: A Case Report

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Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by chronic thrombi in the pulmonary arteries, causing pulmonary hypertension and right heart failure. Early and accurate diagnosis are essential for successful treatment but are often difficult because clinical signs and symptoms can be nonspecific and risk factors, such as history of venous thromboembolism, may not always be present. Here, we report a case involving a 76-year-old woman who demonstrated paradoxical cerebral embolism as the initial manifestation of CTEPH. She developed right hemiplegia without dyspnea or edema. Brain magnetic resonance imaging revealed multiple fresh infarctions, while transesophageal echocardiography revealed a patent foramen ovale. Based on these findings, she was diagnosed as having paradoxical cerebral embolism. During the search for the embolic source, right heart catheterization showed significant pulmonary hypertension and pulmonary angiography revealed chronic thrombi in the peripheral pulmonary arteries, consistent with a diagnosis of CTEPH. To our knowledge, this is the first case of CTEPH to be diagnosed with the onset of paradoxical cerebral embolism. Because CTEPH is the only potentially curable form of pulmonary hypertension, clinicians should consider paradoxical cerebral embolism as a possible initial manifestation of CTEPH.

Key Words: Cryptogenic stroke—chronic thromboembolic pulmonary hypertension—patent foramen ovale—paradoxical cerebral embolism

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by chronic thrombi in the pulmonary arteries, causing pulmonary hypertension and right ventricular dysfunction[1] and is associated with significant morbidity and mortality.[2] However, patients with CTEPH may have no history of pulmonary embolism (PE),[3,4] and CTEPH can develop with nonspecific and insidious clinical symptoms.

Case Report

A 76-year-old woman was referred for dizziness and right-hand clumsiness, which occurred after urination on the previous night. Although she reported slight dyspnea while cycling, ordinary physical activities were not limited and her New York Heart Association Functional Classification was I. She had no history of PE, deep venous thrombosis (DVT), or atrial fibrillation.

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On admission, her blood pressure was 131/85 mmHg, heart rate was 74 beats/min, and respiratory rate was 18 breaths/min. No pathologic breath sounds or heart murmurs were heard and no pitting edema was observed in her lower extremities. Neurologic examination revealed right hemiplegia and right-hand numbness. Her National Institutes of Health Stroke Scale score was 2.

Brain magnetic resonance imaging revealed sporadic fresh cerebral infarctions in the left insular cortex and bilateral parietal cortices (Fig 1A). No significant stenosis was observed on brain and carotid magnetic resonance

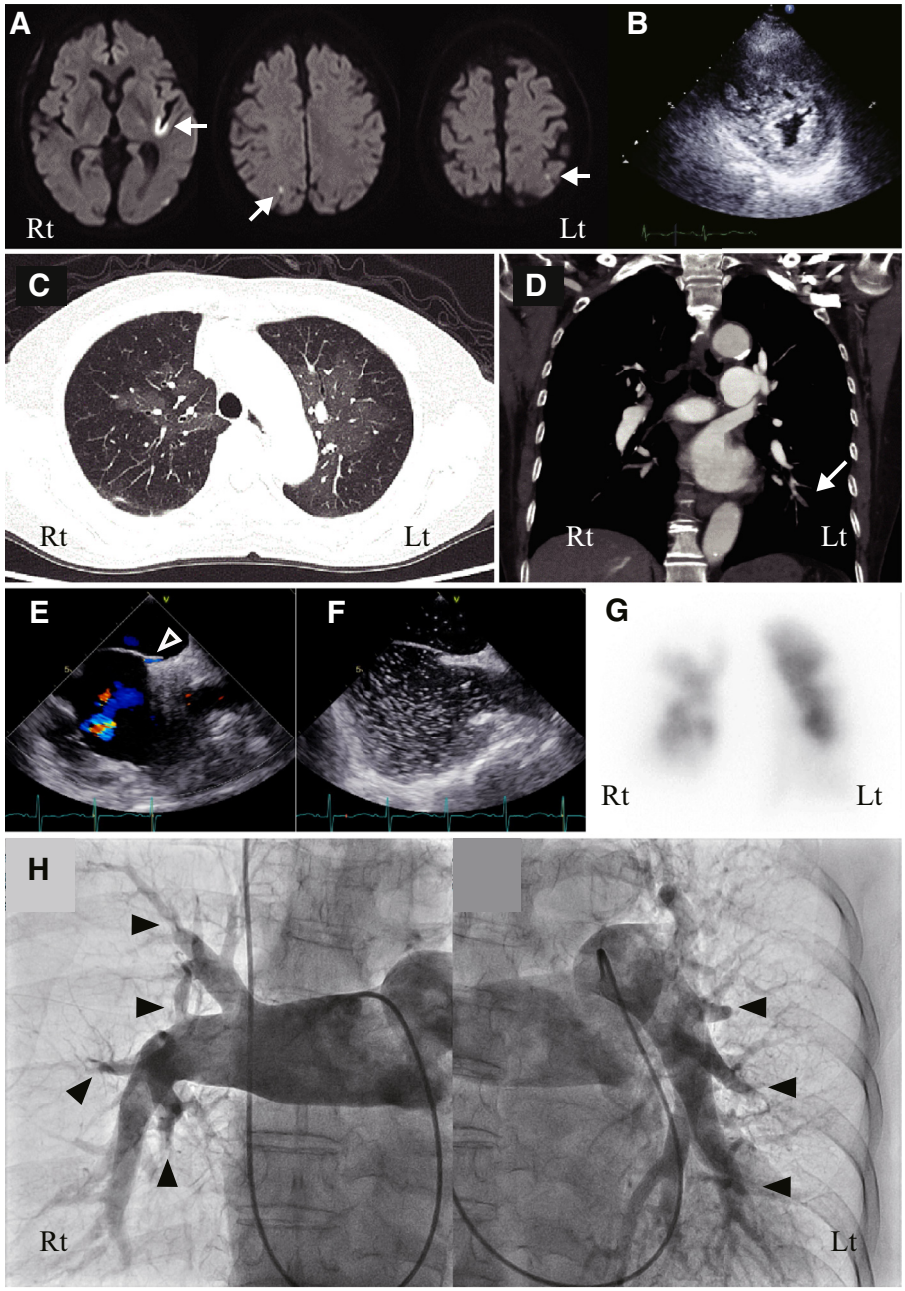

Figure 1. *(A) Axial diffusion-weighted magnetic resonance image on admission showing sporadic acute cerebral infarctions in the left insular cortex and bilateral parietal cortices (arrows). (B) Short-axis transthoracic echocardiogram on admission showing a D-shaped left ventricle due to compression by a markedly dilated right ventricle. (C) Contrast-enhanced computed tomography (CT) scan showing a mosaic perfusion pattern, patchy areas of decreased attenuation intermingled with areas of increased attenuation in bilateral lung fields. (D) Coronal CT pulmonary angiogram showing mural thrombi in the left peripheral pulmonary arteries (arrow). (E) Color Doppler transesophageal echocardiography (TEE) showing color-flow communication (open arrowhead) through a patent foramen ovale (PFO). (F) Contrast-enhanced TEE showing translocation of microbubbles from the right atrium to the left atrium after a Valsalva maneuver, indicating a right-to-left shunt through a PFO. (G) Anterior ventilation/perfusion scan showing unmatched perfusion defects in bilateral lung fields. (H) Pulmonary angiogram showing intimal irregularities and abrupt narrowing of the right pulmonary arteries in addition to pouch defects in the left pulmonary arteries (closed arrowhead), consistent with chronic thromboembolic pulmonary hypertension.*

angiography. Cervical color Doppler ultrasound showed normal arterial morphology and blood flow velocity in the bilateral carotid and vertebral arteries.

Laboratory tests revealed high levels of high-sensitivity troponin I (494 ng/L) and N-terminal pro-brain natriuretic peptide (3009 pg/mL). Although protein C, protein S, antithrombin III, lupus anticoagulant, and anticardiolipin antibodies were within normal limits, her D-dimer level was moderately elevated (4.2 μg/mL). Twelve-lead electrocardiography showed a normal sinus rhythm. Chest radiography revealed an increase in the size of the cardiac shadow, with a cardiothoracic ratio of 54%. Results of pulmonary function tests were within normal limits, but results of arterial blood gas analysis (room air) were consistent with respiratory alkalosis with hypoxia (PaO_2, 52.7 mmHg; $PaCO_2$, 29.2 mmHg; pH, 7.484).

Transthoracic echocardiography revealed a normal ejection fraction (70%) without a patent foramen ovale (PFO). Neither spontaneous echo contrast nor thrombus was detected. However, right heart cavity dilation was observed with a D-shaped left ventricle (Fig 1B) with high tricuspid regurgitation peak gradient (72 mmHg), suggestive of pulmonary hypertension. Twenty-four-hour electrocardiographic monitoring showed a normal sinus rhythm throughout with no atrial fibrillation episodes. Chest contrast-enhanced computed tomography (CT) demonstrated a mosaic perfusion pattern in bilateral lung fields (Fig 1C), while CT pulmonary angiography revealed mural thrombi in the left peripheral pulmonary arteries (Fig 1D).

Color Doppler transesophageal echocardiography revealed a right-to-left shunt at the interatrial septum (Fig 1E), while 2-dimensional transesophageal echocardiography showed right-to-left microbubbles in the left atrium after a Valsalva maneuver (Fig 1F), indicating the existence of a PFO. Ultrasound and contrast-enhanced CT of the lower extremities showed no evidence of DVT; however, a ventilation/perfusion scan revealed unmatched perfusion defects in bilateral lung fields (Fig 1G). Right heart catheterization confirmed significant pulmonary hypertension, with mean pulmonary artery pressure (mPAP) of 38 mmHg, while pulmonary artery wedge pressure was normal (3 mmHg). Furthermore, pulmonary angiography showed intimal irregularities and abrupt narrowing of the right pulmonary arteries in addition to pouch defects in the left pulmonary arteries (Fig 1H). Finally, a diagnosis of CTEPH complicated by paradoxical cerebral embolism was made.

The patient had no indication for pulmonary endarterectomy or balloon pulmonary angioplasty and was administered warfarin and riociguat (3 mg/d) for the treatment of pulmonary hypertension. She had no recurrence of cerebral infarction within 6 months of follow-up and her pulmonary hypertension gradually improved. Her tricuspid regurgitation peak gradient decreased to 52 mmHg and she felt no dyspnea on exertion.

Discussion

To our knowledge, this is the first case of CTEPH to be diagnosed with the onset of paradoxical cerebral embolism.

Venous thrombosis may cause embolism in both the lungs and brain if a PFO exists.[5-7] Unlike those with acute PE, however, approximately half of patients with CTEPH have no history of DVT, and D-dimer levels are increased in only about one-quarter of cases.[8] Therefore, pulmonary hypertension is the key echocardiographic finding for CTEPH diagnosis. Without appropriate treatment, CTEPH has an estimated 5-year survival rate of 30% in patients with mPAP >40 mmHg and 10% in patients with mPAP >50 mmHg.[3] Although rare, it is necessary to consider CTEPH as a comorbidity that causes paradoxical cerebral embolism.

CTEPH is the only potentially curable form of pulmonary hypertension.[3] Pulmonary endarterectomy is considered curative for CTEPH with central pulmonary thrombi, while balloon pulmonary angioplasty is available for more distal thrombi. In addition, riociguat, a novel pulmonary vasodilator that acts via stimulation of soluble guanylate cyclase, is approved for patients with inoperative CTEPH. Considering the prevention of paradoxical cerebral embolism in patients with CTEPH and a PFO, correction of pulmonary hemodynamics is important in addition to anticoagulation.

It has been reported that the prevalence of new ischemic brain lesions in patients with PE is related to the presence of a PFO and right-to-left shunt, suggesting a higher risk of paradoxical embolism in those patients despite effective oral anticoagulation.[9] As a possible explanation, it is assumed that higher right-sided pressure and dysfunction may predispose to more right-to-left shunting owing to a previously closed foramen ovale becoming stretched open with disease progression.[10] Confirmation via large-scale studies is necessary.

Conclusions

It is important to recognize that paradoxical cerebral embolism can develop as a rare initial manifestation of CTEPH. Furthermore, in terms of secondary cerebral embolism prevention, simultaneous correction of pulmonary hemodynamics and anticoagulation is important.

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