CASE PRESENTATION

Cascade of arterial and venous thromboembolic events with multiple possible etiologies

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Abstract: Introduction – The diagnostic workup of simultaneous systemic and pulmonary embolisms is always challenging. We report a notable case of multiple, life-threatening, successive systemic and pulmonary thromboembolic events with multiple possible etiologies. Case report – A 78-year-old hypertensive male presented to the Emergency Department with acute left upper limb ischemia and intermediate risk pulmonary embolism (PE) probably dating for three days, complicated by left-sided ischemic stroke two days after hospital admission, despite well-conducted anticoagulant therapy. The diagnostic workup revealed a history of permanent atrial fibrillation (AF) and no ambulatory anticoagulant treatment, and carotid atherosclerotic disease. Echocardiography revealed the presence of a patent foramen ovale (PFO). After transbrachial embolec- tomy and under anticoagulant treatment PE evolution was favorable, the left upper limb was fully recovered, but there was no improvement of his neurological status. Conclusions – In the present case, the coexistence of multiple prothrombotic conditions makes it impossible to establish an etiologic diagnosis. Embolization from a deep vein thrombosis into both pulmonary and systemic circulations, through the PFO, may have been responsible for the entire spectrum of embolic events. Alternatively, systemic embolic events may have been linked to arterial atherosclerotic lesions or AF, whereas AF-related right atrial thrombosis may have caused PE. Keywords: acute limb ischemia, stroke, pulmonary embolism, atrial fibrillation, deep vein thrombosis

INTRODUCTION

Arterial and venous thromboses are considered as distinct conditions, with different pathophysiological substrates1. Meanwhile, embolism may cause both systemic and pulmonary arterial occlusion. Simultaneous systemic and pulmonary embolic events may occasionally be seen in clinical practice. The diagnostic workup of such cases is often challenging.

In more than half of cases, pulmonary embolism (PE) is caused by thrombi that originate in the deep venous system of the lower extremities2 and rarely in the pelvic or renal territories, or in the right heart chambers. Systemic embolisms on the other hand mainly arise from cardiac thrombi, frequently associated with atrial fibrillation (AF) or left ventricular aneurysm, cardiac tumors or endocarditis, or from complicated atherosclerotic lesions of the aortic arch3. Concomi-
tant pulmonary and systemic embolic events are often related to paradoxical embolisms occurring in the setting of a patent foramen ovale (PFO) or atrial septal aneurysms. Recurrence of embolisms despite well-conducted anticoagulant therapy may result from multiple causes, including mobile thrombi in the cardiac chambers, the aortic arch, or in the deep vein system.

We report a notable case of multiple, life-threatening, successive systemic and pulmonary thromboembolic events with multiple possible etiologies.

**CASE REPORT**

A 78-year-old Caucasian male presented to the Emergency Department for atypical chest pain associated with acute, severe pain and functional impotence of the left upper limb. The onset of symptoms was three days earlier, with rest dyspnea, atypical chest pain, dizziness, cough, and excessive sweating. His medical history revealed arterial hypertension and permanent AF (CHA2DS2-VASc score = 3). The patient was not taking any anticoagulant treatment.

Physical examination revealed cyanosis of the left upper limb associated with paresthesia, paralysis and pulselessness at the left brachial, ulnar and radial arteries. The pulse was present at all other usual sites. Cardiac examination revealed tachycardic (90 bpm), irregular heartbeats. The blood pressure at the right upper limb was 145/100 mmHg. Ventilatory rate was 28 breaths/min, with an O₂ saturation of 80% that rose to 90% when O₂ was administered via simple O₂ mask; lung auscultation was normal. The ECG revealed AF with negative T waves in leads V₁-V₅ (Figure 1). Blood gases analysis showed hypoxia with normocapnia and mild respiratory alkalosis (pH 7.51). D-dimer test was positive and troponin I was slightly elevated (0.036 ng/mL). Computed tomographic (CT) angiography of the chest, abdomen, pelvis and left upper limb showed the presence of large emboli in both right and left pulmonary arteries (Figure 2A) and total occlusion of the left subclavian artery (Figure 2B), without any other abnormalities.

Given the double systemic and pulmonary embolic event, the patient was started on intravenous unfrac-
ultrasonationed heparin. Since the patient was hemodynamically stable and presented severe limb ischemia with recent onset and viable limb, emergent embolectomy by transbrachial approach, using the Fogarty catheter, was performed. Heparin was continued postoperatively and the patient was admitted to the Cardiology Department.

Complete blood count, renal and liver function and electrolyte balance showed no significant abnormalities. Tumor markers including the prostate-specific antigen, the cancer antigen 19-9 and the carcinoembryonic antigen were within normal limits. Transthoracic echocardiography revealed a non-dilated left ventricle with mild impairment of the ejection fraction (45%), mild aortic regurgitation and moderately enlarged right ventricle (Figure 3). The right ventricle displayed moderately impaired systolic function that spared the right ventricular apex. There was moderate tricuspid regurgitation and systolic pulmonary artery pressure was 60 mmHg. Color Doppler imaging revealed the presence of a PFO (Figure 4A), confirmed by contrast echocardiography (Figure 4B). Doppler ultrasonography of the lower limbs was scheduled 48 h later. After initially stable clinical evolution, 32 h later, the patient presented sudden onset right hemiparesis and mixed aphasia. Cranial CT scan at the onset of symptoms, repeated 72 h later, confirmed the presence of a large left-sided ischemic stroke (Figure 5). The patient was transferred to the Neurology Department. Doppler ultrasound examination of the carotid and vertebral arteries revealed a 30% stenosis at the origin of the right internal carotid artery and total occlusion of the left internal carotid artery. The patient was discharged two weeks after the cerebral event on oral anticoagulation, aspirin, rate control for AF, and antihypertensive treatment. By the time of discharge the patient was hemodynamically stable, did not require $O_2$ therapy, the left upper limb was fully recovered, but there was no improvement of his right hemiparesis and mixed aphasia. Follow-up at three months revealed no other thrombotic events, but there was still no improvement of his neurological sequelae.

DISCUSSION

Patients presenting with multiple embolic events are rather commonly seen in clinical practice, but the diagnostic workup is always challenging in such cases. Our patient presented with acute ischemia of the left upper limb associated with intermediate risk pulmonary embolism probably dating for three days, complicated by ischemic stroke two days after hospital admission. Several mechanisms may be taken into account to explain these successive thrombotic events.

The association between PE and deep vein thrombosis (DVT) is well established, the two sharing the same risk factors, including immobility, older age, history of smoking, malignancy, thrombophilia, or post-operative states. Doppler ultrasound evaluation of the...
lower limbs was not performed during hospital stay in our patient, because of the acute, severe neurological event. Although there were no clinical signs of DVT, its presence cannot be ruled out, knowing that clinically apparent DVT is only present in up to 11% of PE cases. On the other hand, in the setting of PE, the source of emboli is often never identified because of thrombus dislodgement in the pulmonary circulation, so that the remaining is too small to be detected. Therefore, the lack of detection of DVT does not necessarily rule out this condition as cause of PE.

Additionally, DVT could also have been the source for systemic embolism. This hypothesis is supported by the finding of a PFO on echocardiography. A PFO can be identified in up to 25% of the adult population and can serve as a route for paradoxical embolization. The presence of a PFO has been incriminated in the occurrence of cryptogenic strokes among young patients, but its role in elderly individuals remains unclear. In patients with intermediate-risk PE, the presence of PFO has been associated with an increased risk of ischemic strokes. Although PFO-related paradoxical embolization usually causes strokes or peripheral ischemia, coronary, renal or splenic ischemic events have also been reported. A PE can be demonstrated in up to 85% of diagnosed cases of paradoxical embolism. A thrombus trapped in the PFO may also explain the occurrence of ischemic stroke during anticoagulation therapy in our patient.

Thus, direct concomitant embolization originating from a DVT into the pulmonary and systemic circulations, through the PFO, may be responsible for the occurrence of both pulmonary and systemic embolic events. Alternatively, the increased right atrial pressure secondary to the PE, which anamnestically preceded the systemic embolic events, may have promoted the opening of the PFO, setting the route for subsequent paradoxical embolization and systemic embolic events.

One should not forget, however, that the patient had permanent AF with an important embolic risk according to the CHA2DS2-VASc score and no anticoagulation. While AF-related left atrial thrombosis could have caused acute limb ischemia and stroke, right atrial thrombosis may have caused PE. Indeed, AF is generally accepted as an independent predictor for systemic embolism, most AF-related systemic embolic events being cerebral (85% of cases) and less peripheral (15%) even after initiation of anticoagulant treatment, the risk of embolization remains high for a few days. On the other hand, the relationship between AF and PE remains controversial, but anatomopatho-
Cascade of thromboembolic events makes it impossible to establish with certainty an etiologic diagnosis. Whereas AF and arterial atherosclerotic lesions, and DVT are widely accepted risk factors for systemic and pulmonary embolisms, respectively, further studies will have to establish the relationship between AF-related right atrial thrombosis and PE.

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References

CONCLUSION
This report illustrates a case of multiple, life-threatening, successive systemic and pulmonary thromboembolic events with multiple possible etiologies. The coexistence of multiple conditions known for their prothrombotic potential makes it impossible to establish with certainty an etiologic diagnosis. Whereas AF and arterial atherosclerotic lesions, and DVT are widely accepted risk factors for systemic and pulmonary embolisms, respectively, further studies will have to establish the relationship between AF-related right atrial thrombosis and PE.