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 embolectomy 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

Rezumat: **Introducere –** Strategia diagnostică în evenimentele embolice simultane sistemice și pulmonare este întotdeauna dificilă. Prezentăm un caz de evenimente embolice sistemice și pulmonare multiple, succesive, cu multiple posibile etiologii. **Prezentare de caz –** Un pacient de sex masculin de 78 de ani, hipertensiv, s-a prezentat la Serviciul de Urgență cu ischemie acută de membru superior stâng și embolie pulmonară (EP) datând probabil de trei zile, complicate cu accident vascular cerebral ischemic silvian stâng la două zile după internare, în ciuda terapiei anticoagulante. Evaluarea diagnostică a evidențiat fibrilație atrială (FA) permanentă fără tratament anticoagulant ambulatoriu și ateroscleroză carotidiană. Ecocardiografia a evidențiat prezența unui foramen ovale patent (FOP). După embolectomie transbrahială și sub tratament anticoagulant evoluția EP a fost favorabilă, s-a obținut recuperarea completă a membrului superior, dar nu și ameliorare neurologică. **Concluzii –** În cazul de față, coexistența a multiple afecțiuni protrombotice face imposibilă stabilirea unui diagnostic etiologic. Embolizarea dintr-o tromboză venoasă profundă atât în circulația pulmonară cât și în cea sistemică, prin FOP, ar putea fi responsabilă de toate evenimentele embolice. Pe de altă parte, evenimentele embolice sistemice ar putea fi legate de leziunile aterosclerotice arteriale sau de FA, în timp ce tromboza atrială dreaptă în contextul FA ar putea fi cauza EP.
Cuvinte cheie: ischemie acută de membru, accident vascular cerebral, embolie pulmonară, fibrilație atrială, tromboză venoasă profundă

INTRODUCTION

Arterial and venous thromboses are considered as distinct conditions, with different pathophysiological substrates[1]. 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 extremities[2] 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 arch[3]. Concomi-

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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[4]. 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[1].

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 (CHA_2DS_2-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 O_2 saturation of 80% that rose to 90% when O_2 was administered via simple O_2 mask; lung auscultation was normal. The ECG revealed AF with negative T waves in leads V_1-V_5 (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-

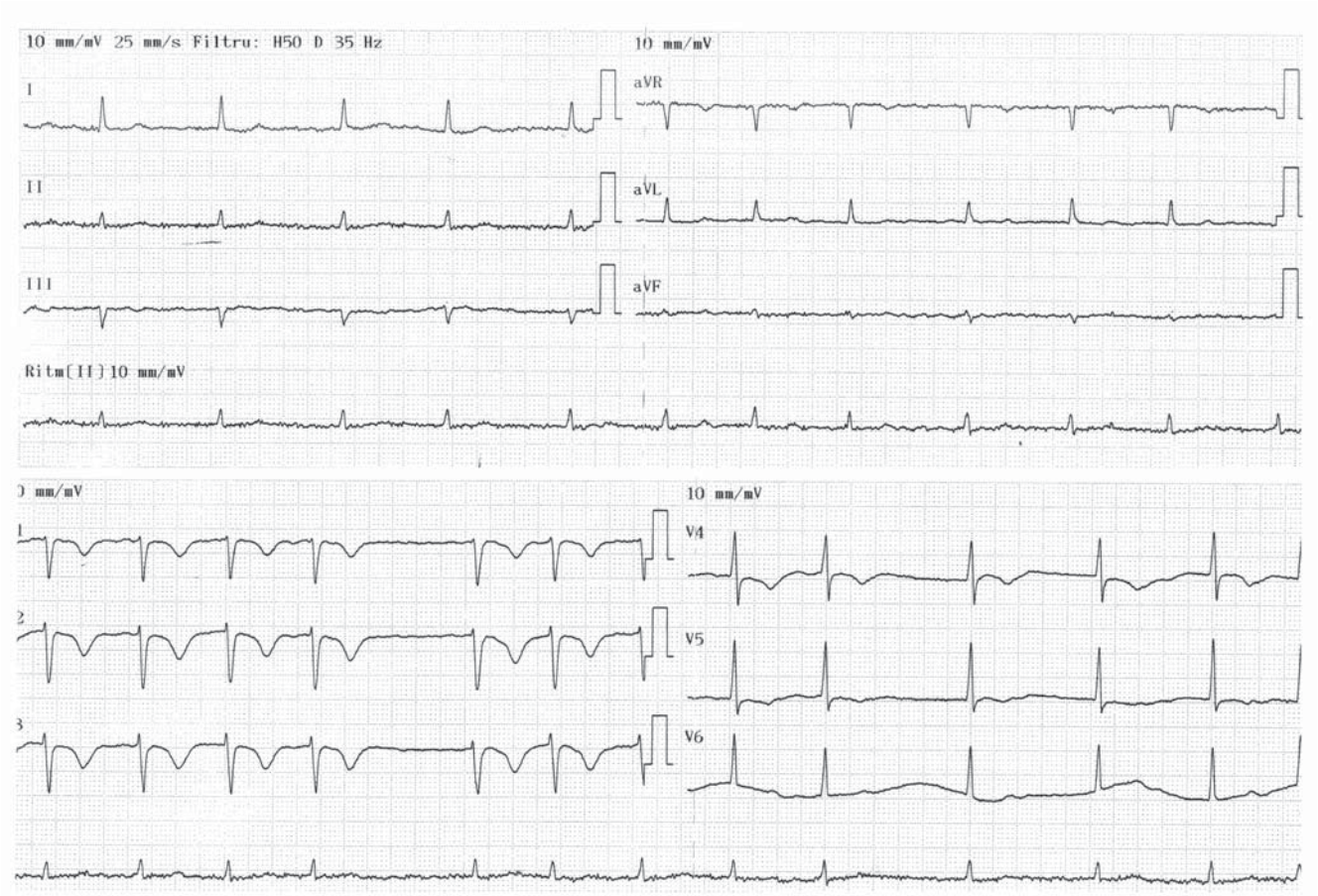

Figure 1. ECG tracing showing atrial fibrillation and negative T waves in leads V_1 to V_5.

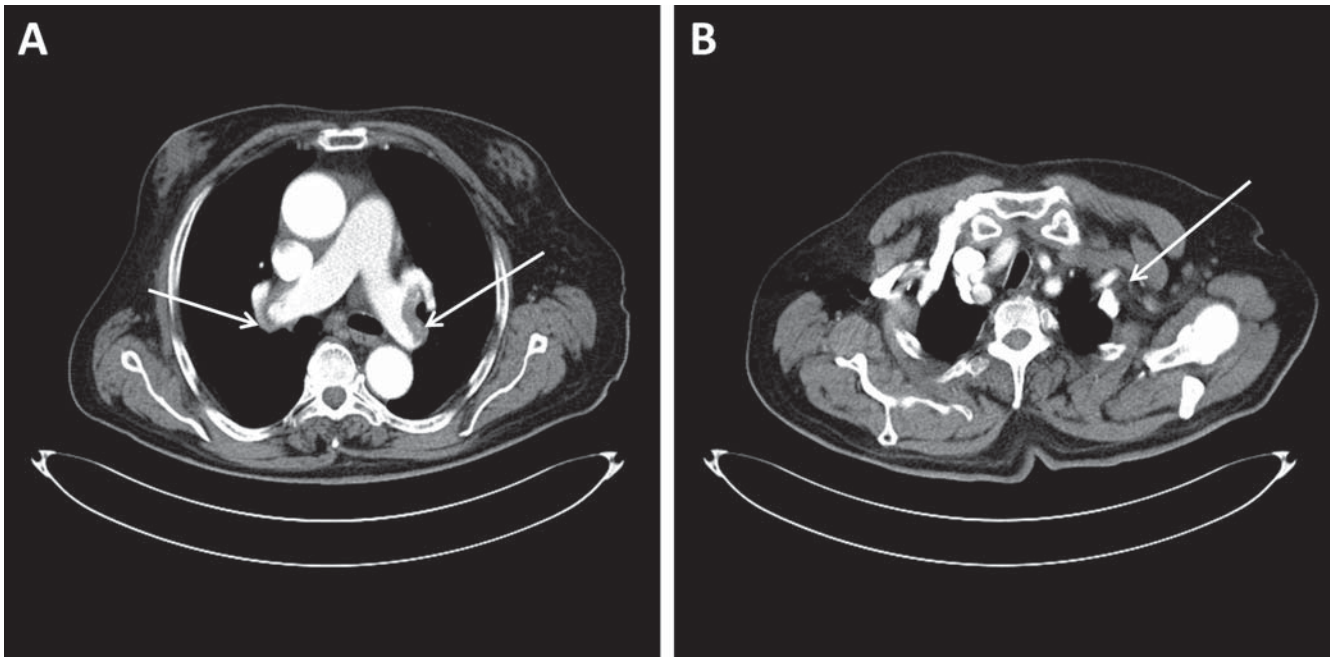

Figure 2. Computed tomographic angiography images of the chest showing (A) large emboli in both right and left pulmonary arteries (arrows) and (B) total occlusion of the left subclavian artery (arrow).

tionated 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 postoperative states[5]. Doppler ultrasound evaluation of the

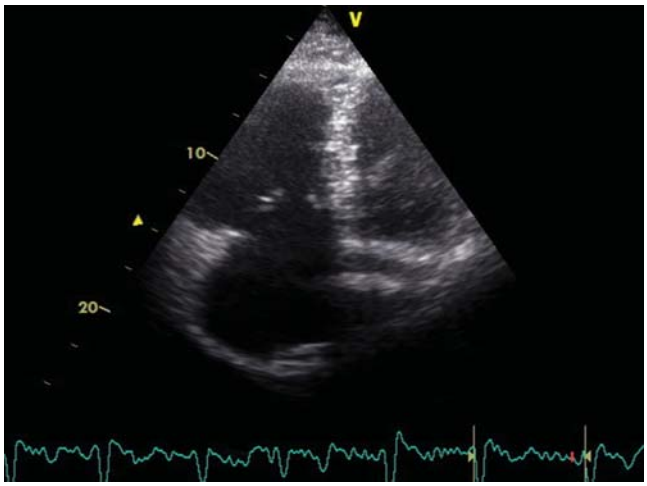

Figure 3. Transthoracic echocardiographic B-mode image in apical view showing moderately dilated right ventricle.

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[6,7]. 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[8]. 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[4]. In patients with intermediate-risk PE, the presence of PFO has been associated with an increased risk of ischemic strokes[9]. 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[10]. A thrombus trapped in the PFO may also explain the occurrence of ischemic stroke during anticoagulation therapy in our patient[11].

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 CHA_2DS_2-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[12]. Indeed, AF is generally accepted as an independent predictor for systemic embolism[13], most AF-related systemic embolic events being cerebral (85% of cases) and less peripheral (15%)[14]. 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-

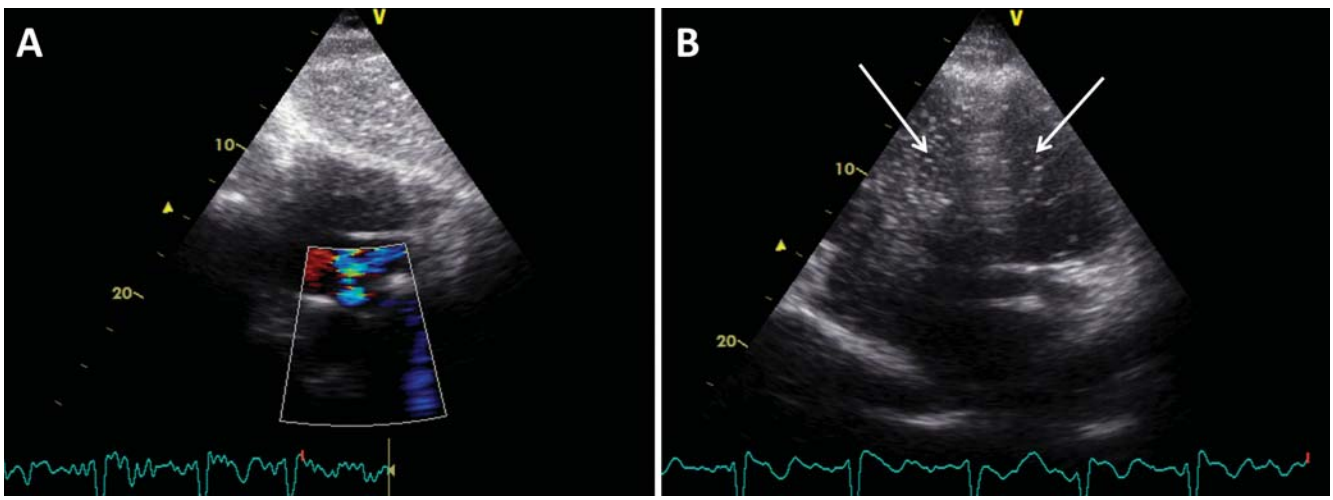

Figure 4. Transthoracic (A) color Doppler image in subcostal view and (B) contrast echocardiographic image in apical view showing a patent foramen ovale with right-to-left shunt. Note the presence of contrast echoes, depicted as white pixels, in both the right and left ventricles (arrows).

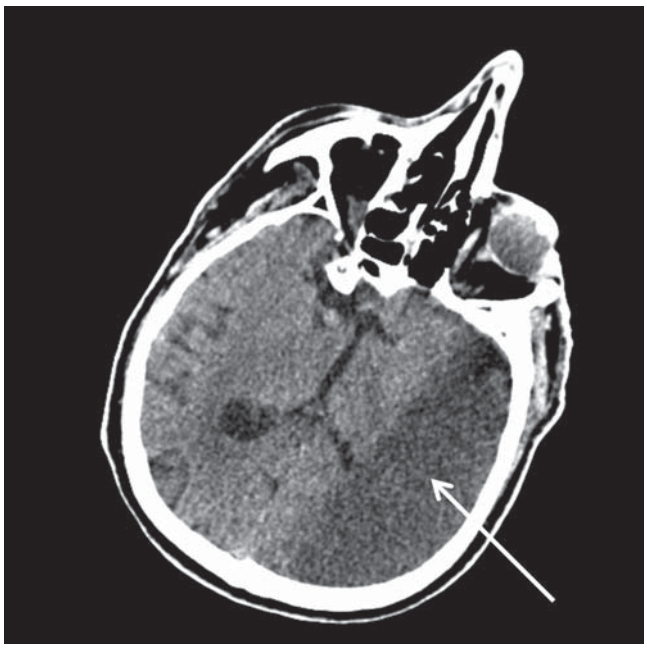

Figure 5. Computed tomography image of the brain showing left-sided ischemic stroke (arrow).

logical studies suggest that right atrial thrombosis might have a similar role for the development of PE as left atrial thrombosis for systemic embolism. A recent autopsy-based study demonstrated that right intracardiac thrombosis is as common as left intracardiac thrombosis[8]. However, due to inaccessibility of the right heart to non-invasive diagnostic techniques, large-scale in vivo studies assessing the prevalence of right atrial thrombosis among AF patients and the associated PE risk are still lacking.

Finally, the multiple systemic and pulmonary embolic events in our patient may have been fully independent. Whereas a DVT could have been responsible for the PE, the double systemic embolic event may have been caused by dislocation of left atrial thrombi in the setting of permanent AF or by embolization from arterial sources.

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.

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