**Title:** A rare presentation of multi-organ embolism in a multifactorial hypercoagulable state – case report.

**Título**: Uma apresentação rara de embolia multiorgânica num estado de hipercoagulabilidade multifatorial – caso clínico.

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**Abstract**

Paradoxical embolism is an uncommon phenomenon, accounting for only 2% of all cases of systemic arterial embolism. This condition suggests the presence of a patent foramen ovale, present in 20-25% of the adult population. The authors report a case of a 63-year-old male patient with a history of lung adenocarcinoma and hereditary thrombophilia admitted to hospital with acute onset of dyspnea, diplopia, confusion and decreased strength of the right limbs. Cranial computed tomography scan showed stroke in the left posterior cerebral artery and computed tomography pulmonary angiography revealed bilateral pulmonary thromboembolism. A transesophageal echocardiogram confirm the presence of patent foramen ovale. The patient was treated with anticoagulant therapy with progressive clinical improvement. Due to a high risk of recurrent thromboembolic episodes the percutaneous closure of patent foramen ovale was performed and the anticoagulant therapy was maintained indefinitely.

***Key words:*** *paradoxical embolism, patent foramen ovale, lung cancer, hereditary thrombophilia*

**Resumo:**

A embolização paradoxal é um fenómeno incomum, correspondendo apenas a 2% de todos os casos de embolia sistémica arterial. Esta condição sugere a presença de foramen ovale patente, presente em 20-25% da população adulta. Os autores relatam um caso de um homem de 63 anos, com os diagnósticos prévios de adenocarcinoma do pulmão e trombofilia hereditária, admitido no hospital com quadro agudo de dispneia, diplopia, confusão e diminuição da força dos membros à direita. A tomografia computorizada crânio-encefálica mostrou isquémica cerebral na região da artéria cerebral posterior esquerda e a angiotomografia computorizada torácica revelou tromboembolismo pulmonar bilateral. O ecocardiograma transesofágico confirmou a presença de foramen ovale patente. O doente foi tratado com terapêutica anticoagulante com melhoria clínica progressiva. Devido ao elevado risco de recorrência de eventos tromboembólicos, o doente foi submetido a encerramento percutâneo do foramen ovale patente e a anticoagulação foi mantida por tempo indeterminado.

***Palavras-chave:*** *embolização paradoxal, foramen ovale patente, cancro do pulmão, trombofilia hereditária*

**Introduction:**

Paradoxical embolism is an uncommon phenomenon, accounting for only 2% of all cases of systemic arterial embolism. This condition suggests the presence of a patent foramen ovale (PFO), present in 20-25% of the adult population. PFO is usually asymptomatic, but when associated with states of hypercoagulability the risk of systemic embolization is significant.1,2 Hereditary thrombophilia and other states of hypercoagulability, as those related to neoplastic diseases, increase the risk of thromboembolic events.3,4 Commonly the embolic phenomenon occurs in the pulmonary circulation but in the presence of a PFO, with a right to left shunt, cryptogenic strokes may occur. Ischemic strokes cause significant morbidity and mortality and the direct causal relationship between PFO and hypercoagulability states is sometimes difficult to establish. However, this relation may account for a proportion of cryptogenic stroke cases and should always be investigated.2,5

**Case report**

We report a case of a 63-year-old male patient presented to the emergency department with acute onset of dyspnea, mental confusion, diplopia and decreased muscle strength of the right limbs. The patient was a former smoker and his medical background included factor V Leiden thrombophilia, identified in the context of screening due to family history of recurrent thrombosis. The patient has also recent diagnosis of lung adenocarcinoma, stage IA2 with microvascular invasion (pT1bN0M0 of the TNM classification-8th edition), submitted to left upper lobectomy 5 months prior to admission and completed the last cycle of adjuvant chemotherapy (cisplatin-vinorelbine regimen) 6 days before admission.

The physical examination revealed polypnea, tachycardia (heart rate of 120 beats per minute), blood pressure 126/76mmHg and an oxygen saturation of 91% with FiO2 44% of oxygen supplementation (PaO2/FiO2 ratio=114). No abnormalities in thoracic, abdominal, and limb examination were found. Neurologically there was a right homonymous hemianopsia, central right facial palsy, alexia, pain and proprioceptive sensitivity decrease, hemiparesis with sensory ataxia of right limbs and abnormal right plantar reflex.

The 12 leads electrocardiogram revealed a S1Q3T3 pattern. Cranial computed tomography (CT) scan showed a left temporo-occipital hypodensity, without mass effect, suggestive of acute ischemic injury in the territory of the left posterior cerebral artery (Fig.1). The CT pulmonary angiography (Fig.2) reveled an endoluminal repletion defect in the distal left pulmonary artery, intermediate artery and bilateral lobular branches, with extension to some segmental and sub segmental branches, compatible with pulmonary thromboembolism. Doppler ultrasound of lower extremities revealed thrombosis in the right posterior tibial vein. Transthoracic echocardiography performed at the bedside (without doppler) demonstrated dilated right heart cavities with preserved systolic function (TAPSE 19mm). The cardiac laboratory biomarkers were negative.

The patient was hospitalized with the diagnoses of pulmonary embolism of intermediate-low risk (PESI class V and signs of right ventricular dysfunction), acute stroke and deep venous thrombosis.

At admission it was instituted anticoagulation with low-molecular-weight-heparin (LMWH) 1 mg/Kg twice daily together with antiplatelet therapy. Due to the risk of cerebral hemorrhagic transformation, the antiplatelet therapy was discontinued 72 hours after admission. Owing to a high suspicion of paradoxical embolism a contrast transesophageal echocardiography was performed which revealed the presence of a PFO with a small right-to-left shunt and no evidence of intra-cardiac masses or thrombi. Clinical improvement was observed throughout the hospitalization and the patient was discharged after 34 days of anticoagulation therapy. Percutaneous closure of the PFO was performed using an AmplatzerTM PFO Occluder 25mm device. The anticoagulant therapy was maintained indefinitely with LMWH in full doses. At 6-month follow up visit the patient remained in rehabilitation program due to residual neurological sequelae (right homonymous hemianopsia and right hand astereognosis) and no recurrent embolic episodes were observed.

**Discussion:**

This case demonstrates the diagnostic steps and therapeutic approach in face of a patient with multiple thromboembolic events. The presence of several risk factors such as thrombophilia and lung cancer under chemotherapy treatment is likely to confer cumulative risk of venous thromboembolism (VTE).3,4

The overlap cryptogenic stroke associated to pulmonary embolism and deep vein thrombosis is very rare as initial presentation and a high level of suspicious must conduct to an appropriate sequence of investigation and treatment. The contrast transesophageal echocardiography provides visualization of the PFO and can show the shunt itself, and the CT pulmonary angiography confirms the pulmonary embolism.2

For patients with ischemic stroke and both PFO with a venous source of embolism, anticoagulation is indicated. When anticoagulation is contraindicated, an inferior vena cava filter may be performed.5,6 The type of anticoagulation treatment should be made on a case-by-case basis. Clinical guidelines recommend LMWH as first-line treatment of short- and long-term management of cancer-associated VTE.6-8 The VKAs are considered second-line therapy with a higher recurrence rate but a similar bleeding rates ~5%, comparing with LMWH.9 Clinical data supporting new oral anticoagulants (NOACs) use in cancer patients are recently available. Randomized trials have shown that rivaroxaban (for initial and long-term anticoagulation) and edoxaban (for long-term anticoagulation) are safe and effective.7 Those trials gave support to the American Society of Clinical Oncology guidelines on the use NOACs for preventing and treating cancer-associated VTE. Nevertheless, LMWH is preferred over NOACs in patients with increased risk of bleeding or when possible drug interactions are suspected.7,10

Also, the strategy regarding percutaneous transcatheter closure of PFO for secondary stroke prevention is still controversial. Randomized controlled trials have shown that PFO closure reduces stroke recurrence compared with medical therapy alone,11,12 but the evidence has been conflicting due to the different role that PFO can play in different scenarios. Currently the European societies have agreed on performing closure of a PFO in carefully selected patients aged from 18 to 65 years with a confirmed cryptogenic stroke, transient ischemic attack or systemic embolism and an estimated high probability of a causal role of the PFO as assessed by clinical, anatomical and imaging features.13 In our case, being the first thromboembolic episode in active cancer patient with high risk of recurrence and indefinite duration of medical therapy, associated with an increased risk of bleeding due to concomitant stroke, we chose LMWH associated to percutaneous transcatheter closure of the PFO.

**Figure legends:**

Figure 1: Cranial CT showing ischemic injury in the territory of the left posterior cerebral artery.

Figure 2: CT pulmonary angiography showing massive pulmonary embolism.

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