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## **Title page**

# **Recurrence of ischemic stroke on direct oral anticoagulant therapy in a patient with marantic endocarditis related to lung cancer.**

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## **Abstract**

Venous thromboembolism (VTE) and arterial thromboembolism (ATE) are frequent complications in cancer patients. For curative treatment of VTE in a neoplastic context, recent randomized controlled trials and meta-analyses suggest that direct oral anticoagulants (DOACs) can be an alternative to conventional treatment by low molecular weight heparins (LMWHs). On the other hand, the role of DOACs in the treatment of cancer-related ATE still remains unclear. Here, we report a case of stroke recurrence in a patient initially treated with DOACs that were started for cancer-related VTE. The failure of the DOACs, compared to LMWHs, to prevent the stroke recurrence led us to the infrequent final diagnosis of nonbacterial thrombotic endocarditis (NTBE, formerly known as marantic endocarditis). This case illustrates the association between ATE and VTE in a patient with marantic endocarditis related to lung cancer and recurrence of ischemic stroke on direct oral anticoagulant therapy.

**Learning objectives:**

- Arterial (ATE) and venous thromboembolism (VTE) are frequent complications in cancer patients
- ATE and VTE can be responsible for ischemic stroke in neoplastic context
- VTE associated stroke in cancer patients does not exclude ATE etiology (marantic endocarditis)
- Direct oral anticoagulants fail to prevent ischemic stroke associated to marantic endocarditis

## **Main text**

### **Introduction**

For treatment of cancer patients with venous thromboembolism (VTE), guidelines recommend low molecular weight heparin (LMWHs). In recent years, meta-analysis based on indirect comparisons between LMWHs and direct oral anticoagulants (DOACs) suggests that DOACs have similar efficacy and safety to LMWHs for the treatment of cancer-associated thrombosis [1]. However, cancer patients also have a high risk of developing arterial thrombosis with arterial thromboembolism (ATE), caused by both upregulation of coagulation and activation of platelets [2]. The effect of DOACs on the treatment of cancer-related ATE still remains unclear.

Here, we report a case of ischemic stroke recurrences occurring with DOAC treatment administrated for documented VTE, leading to the discovery of marantic endocarditis in a neoplastic context.

### **Case report**

A 64-year-old woman, with no cerebrovascular history, was admitted to the stroke unit for a sudden left hemiparesia. Her medical history recorded a partial thyroidectomy few months ago and active smoking. The patient consulted a clinic because of exertional dyspnea that had been evolving for approximately a month, associated with right calf pain occurred after a long walk a few days prior, leading to the diagnosis of right deep vein thrombosis (solear), complicated by a left distal pulmonary embolism (confirmed at the thoracic CT-scan). CT scan also showed pulmonary nodule requiring more explorations. The patient had normal vital signs (blood pressure 160/80, cardiac frequency 91/minute), including oxygen saturation (ambient air saturation 95%) and no sign of respiratory distress syndrome. Transthoracic echography conducted at this time showed no

cardiopathy or signs of acute right heart failure (only a minor aortic insufficiency). Rivaroxaban 15 mg twice a day was prescribed immediately after the diagnosis.

A day after the initiation of rivaroxaban, she was admitted to our stroke unit because she presented sudden left hemiparesia with dysarthria. The NIHSS score was estimated to be 8, and she had no cardio-respiratory symptoms. A cerebral MRI was performed, showing multi-territorial ischemic strokes with different ages (**Figure 1A**). Indeed, recent ischemic stroke, as diagnosed by a hypersignal on the DWI sequence, were found in the right middle cerebral artery (MCA), right cerebral posterior and bilateral cerebellum territories, and the left superficial-profound MCA junction region. In this context of acute stroke, rivaroxaban was discontinued and treatment with therapeutic doses of intravenous continuous unfractionated heparin (UFH) was initiated immediately.

In the context of multi-territorial ischemic stroke, cardioembolic phenomenon was suspected, particularly paradoxical embolisms occurring during pulmonary embolism. Furthermore, supra-aortic arteries were normal on the CT-scan, cardiac monitoring and biological tests showed no abnormality except for moderate elevation of cardiac troponin (722 ng/l) and D-dimer (35000 ng/ml initially, controlled at 7438 ng/ml after 10 days), related to pulmonary embolism. In particular, no inflammatory syndrome (C-reactive protein 14 mg/l) and thrombophilia tests were all negative (protein C, S, antithrombin III, antiphospholipid antibodies, Factor V Leiden mutation, factor II mutation) and disseminated intravascular coagulation syndrome was absent (Prothrombin Ratio 83%, platelets  $216 \times 10^9/l$ ).

One week later, a neurological exam was stable, so UFH was substituted for DOAC (apixaban 5 mg twice a day). Two days later, the patient presented neurological aggravation with confusion and right hemianopsia. The NIHSS score was calculated to be 11. A new cerebral MRI was performed, showing new ischemic strokes (in DWI sequence), particularly in the left PCA-MCA junction region and the left posterior cerebral artery territory (**Figure 1B**). A treatment with LMWHs was introduced (enoxaparin 0.6 ml twice a day) and apixaban was discontinued.

In this context of recurrent ischemic strokes despite anticoagulation therapy and associated deep vein thrombosis and pulmonary embolism in a patient with no medical history and no thrombophilia at biological tests, with a lung nodule on first CT scan an underlying cancer was suspected. A thoracic-abdominal-pelvic CT-scan was then performed. The pulmonary nodule suspect of malignancy was found, associated to probable secondary liver and bone lesions. A CT scan was followed by a PET scan, which consolidated the hypothesis of cancer (**Figure 2**). Bronchial fibroscopy with nodule biopsy was performed, leading to the diagnosis of primitive pulmonary adenocarcinoma by histological exam.

Given the context of lung cancer with recurrent ischemic strokes despite DOAC therapy, a new transthoracic echocardiography and transesophageal echography (**Figure 3**) was performed to identify a marantic endocarditis, responsible for ATE. These exams showed aortic valvular thickening with a doubt on aortic vegetation on transthoracic echocardiography, not found on transesophageal echography, but with severe aortic insufficiency, confirming the hypothesis of the endocarditis. No patent foramen ovale at bubble tests or interatrial septum aneurysm or interatrial thrombus was observed.

Therefore, in the absence of patent foramen ovale and given the delay between the pulmonary embolism and the onset of neurological symptoms, the hypothesis of paradoxical embolism was disproved. A diagnosis of marantic (non-infectious) endocarditis with ATE was established with transesophageal echography and results of complementary investigations (repeated hemocultures, viral serologies, anti-nuclear auto antibodies, rheumatoid factor) which were all negative.

The neurological exam was constant (NIHSS score of 8 and modified Rankin Scale of 5) and no recurrence of ischemic stroke was observed with enoxaparin, which was continued thereafter. The patient was later hospitalized in oncology for cancer treatment. Unfortunately, the pulmonary adenocarcinoma was already at an advanced stage, so the patient soon had significant cachexia associated with the neurological symptoms. She died a few days after the transfer to oncology, before the initiation of chemotherapy.

## Discussion

This case report illustrates recurrence of ischemic stroke related to marantic endocarditis in a lung cancer context on direct oral anticoagulant therapy. Initially, ischemic strokes were imputed to a VTE phenomenon in neoplastic context. However, two stroke recurrences despite effective anticoagulation by DOACs and the absence of new ischemic lesions during heparin therapy lead us to consider other etiological mechanisms. We imputed an ATE phenomenon in the presence of a marantic endocarditis diagnosed by both transthoracic and transesophageal echography. Recent meta-analysis based on indirect comparisons between LMWHs and DOACs suggest that DOACs have similar efficacy to LMWHs for the treatment of cancer with venous thrombo-embolism [1]. However, these meta-analyses have studied the efficacy of DOACs on the prevention of VTE. In this case, the patient had a right lower extremity deep vein thrombosis complicated by pulmonary embolism, but she also presented marantic endocarditis related to the lung cancer. Indeed, marantic endocarditis can occur in cancer patients, related to a multifactorial hypercoagulability state: procoagulant factors synthesized by cancer cells, thrombogenic treatment and the inflammatory status of the host [2]. They are frequently observed in evolved and multi-metastatic cancer, and especially in adenocarcinoma lung cancer. Histologically, they are composed of fibrinous and platelet thrombus without inflammatory reaction [3]. In fact, we know that cancer patients have a high risk of developing arterial thrombosis with arterial thromboembolism (ATE), caused by both upregulation of coagulation and activation of platelets [2].

Marantic endocarditis is an example of a rare arterial thrombosis which can lead to arterial embolism, and particularly cerebral embolism with ischemic strokes. In the case of ATE in cancer patients, the efficiency of DOACs is unclear. In fact, DOACs are direct thrombin or factor Xa inhibitors which impact the coagulation cascade, but they are insufficient for preventing platelet thrombus. In this case, the patient presented recurrent ischemic strokes with curatives doses of rivaroxaban (first neurologic episode) then apixaban (second neurologic episode), yet she presented



no complications with UFH or LMWHs. A possible explanation for this phenomenon is the insufficiency of DOACs to prevent the formation of platelet thrombus and thus arterial thrombus and ATE, especially in marantic endocarditis. At the opposite, heparin therapies have pleiotropic effects, exerting several antithrombotic effects, beyond their ability to irreversibly inactivate both activated factor Xa and thrombin [2]. Those pleiotropic effects may help prevent ATE events in patients with cancer. Furthermore, randomized controlled trials have only studied the efficacy of edoxaban and rivaroxaban for the treatment of cancer with venous thrombo-embolism.

In cancer patients with marantic endocarditis, the treatment is those of the underlying neoplasia and curative anticoagulation with heparin [3]. The role of DOACs in this context still remains to be defined. Two other cases of recurrent cerebral embolism in cancer patients with marantic endocarditis treated with DOACS have been described in the literature [4, 5]. Our case report enriches the scarce literature on the subject. We conclude that one should systematically consider marantic endocarditis in stroke patients related cancer and eliminate DOAC treatment to prevent ischemic stroke in this context.

## **Conclusions**

Neoplasia associated with VTE and ATE can be responsible for ischemic stroke. The association of VTE and ischemic stroke in cancer patients does not exclude the presence of an ATE phenomenon. Marantic endocarditis diagnosis must be considered particularly in the context of recurrence of ischemic stroke on direct oral anticoagulant therapy.

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**Conflict(s) of Interest**

The Authors declare that there is no conflict of interest.

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## Figures legend

**Figure 1:** (A) Cerebral diffusion MRI: ischemic strokes in MCA territory and superficial-profound MCA junction region. (B) Cerebral diffusion MRI: ischemic strokes in MCA territory, superficial-profound MCA junction region and left cerebral posterior artery-MCA junction region. (C) MRA (3D TOF) : no occlusion of arteries.

**Figure 2:** PET-scan: hypermetabolic pulmonary nodule associated with hypermetabolic mediastino-hilar lymphadenopathies, carcinomatous lymphangitis and hypermetabolic hepatic and bone lesions.

**Figure 3:** Transesophageal echography: aortic valvular thickening (A) without vegetation and major aortic insufficiency (B,C,D).





