CASE PRESENTATION

Anticoagulation therapy for secondary stroke prevention in a patient with active malignancy and non-valvular atrial fibrillation

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Abstract: **Introduction –** The choice of anticoagulation in cancer patients with atrial fibrillation (AF) and stroke remains challenging. Data on direct oral anticoagulant (DOAC) treatment for this group of patients is scarce. **Case report –** A 73-year old woman with a history of malignancy, AF and ischemic stroke was admitted for dysarthria. She had stopped anticoagulation for one year because of haematuria due to bladder cancer relapse. Brain imaging techniques confirmed acute ischemic lesions in multiple vascular territories, and no haemorrhage. Transoesophageal echocardiography showed a mobile thrombus in left atrial appendage. We decided to restart oral anticoagulation and opted for apixaban. **Discussions –** There are no clear guidelines for anticoagulant therapy in patients with cancer and stroke. Several characteristics support DOACs as a choice for long-term treatment: shorter half-life compared to VKAs, lower risk of intracranial bleeding, less food or drug interactions, easier administration and no need for INR control. An exploratory analysis in the ARISTOTLE trial of AF patients and active or a history of cancer showed the superior safety and efficacy with apixaban versus warfarin among patients with and without cancer. **Conclusion –** The underlying malignancy is associated with a higher risk both for bleeding and prothrombotic state and DOACs may be a reasonable choice in this category of patients.
Keywords: Atrial fibrillation, stroke, cancer, direct oral anticoagulant.

Rezumat: **Introducere –** Alegerea terapiei anticoagulante orale la pacienții cu cancer care asociază fibrilație atrială și accident vascular cerebral (AVC) ischemic este controversată. Datele despre tratamentul cu anticoagulantele orale directe (DOAC) la acești pacienți sunt limitate. **Prezentarea cazului –** O femeie în vârstă de 73 de ani, cunoscută cu cancer, fibrilație atrială și AVC ischemic în antecedente se prezintă pentru dizartrie nou instalată. Tratamentul anticoagulant oral a fost oprit în urmă cu 1 an, după un episod de hematurie, moment în care s-a diagnosticat recidiva de cancer a vezicii urinare. Investigațiile imagistice au arătat prezența unor leziuni ischemice acute în multiple teritorii vasculare, fără hemoragie. Ecografia transesofagiană a evidențiat tromboză auriculară stângă. Tratamentul anticoagulant oral a fost reluat cu apixaban. **Discuții –** În prezent, nu există dovezi și recomandări clare privind anticoagularea orală la pacienții care asociază cancer, fibrilație atrială și AVC ischemic. Tratamentul cu DOAC poate fi luat în considerare, având în vedere timpul de înjumătățire mai scurt decât al antivitaminelor K, riscul mai mic de sângerare intracraniană, interacțiunile medicamentoase și alimentare mai puține, ușurința administrării și lipsa monitorizării INR-ului. O subanaliză a studiului ARISTOTLE la pacienții cu fibrilație atrială, istoric de cancer sau cancer activ a demonstrat eficacitatea și siguranța tratamentului cu apixaban vs. warfarina la pacienții cu sau fără cancer. **Concluzie –** Cancerul este o boală care asociază un risc mai mare atât de embolie, cât și de sângerare. Tratamentul cu DOAC ar putea fi luat în considerare la acești pacienți.
Cuvinte cheie: fibrilație atrială, accident vascular cerebral, cancer, anticoagulant oral direct.

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INTRODUCTION

Oral anticoagulation therapy in patients with active malignancy and atrial fibrillation (AF) is challenging. The rate of stroke in patients with cancer seems to be higher compared to general population[1], and both cancer and AF are independent risk factors for ischemic stroke. Thus, anticoagulation therapy must be considered in these patients. However, higher bleeding risk associated with cancer leads to an underuse of oral anticoagulation in patients with malignancies[2]. Moreover, data on direct oral anticoagulant (DOAC) treatment for this group of patients is scarce. Our aim was to address the issue of DOAC therapy for secondary stroke prevention in a patient with active malignancy and non-valvular AF.

CASE PRESENTATION

A 73-year old hypertensive, diabetic woman presented in the emergency department with new onset dysarthria. Her medical history started sixteen years ago, when she was diagnosed with endometrial cancer, surgically treated. Two years later, urinary bladder cancer was diagnosed, followed by surgery and chemotherapy. The patient was symptom free up to one year ago, when she suffered an acute ischemic stroke and was found in atrial fibrillation. Anticoagulation therapy with dabigatran 150 mg BID was initiated. The patient presented haematuria while on DOAC treatment. Bladder cancer relapse was diagnosed, and dabigatran was stopped. She presented with dysarthria in the emergency department, one year after having stopped treatment with dabigatran.

Resting 12-lead electrocardiogram showed AF with normal ventricular rate. Laboratory tests revealed mild microcytic hypochromic anaemia (Hb=9.7 g/dL, Ht=27%, MCV=72 fL, MCH=22 pg), confirmed by blood smear with a low ferritin level (100 pg/mL), and no other significant changes. Brain computed tomography in the emergency room showed multiple chronic sequelae, with no recent lesions and no haemorrhage (Figure 1). However, diffusion magnetic resonance imaging (MRI) revealed three acute ischemic lesions in multiple vascular territories (Figure 2). Carotid ultrasound showed non-significant stable atherosclerotic plaques. However, frequent bilateral microembolic signals were detected using transcranial Doppler (Figure 3). These findings did not support an atherothrombotic mechanism for stroke, but suggested cardioembolism as a cause for this event. The patient was referred for transoesophageal echocardiography (TEE), as part of the diagnostic work-up, showing a mobile thrombus in the left atrial appendage (Figure 4).

In summary, our patient had a history of recurrent cardioembolic ischemic strokes, some symptomatic, some asymptomatic, in multiple vascular territories, with a CHA_2DS_2-VASc score of 8 and a HAS-BLED risk of 3. We decided to restart oral anticoagulation and opted for apixaban 5 mg BID, taking into consideration normal renal function, no recent bleed, patient functional impairment (Karnofsky Performance Scale Index 60%) and preference. The patient was discharged with no further complications and remained stable at one year follow up.

DISCUSSION

Atrial fibrillation and cancer often coexist, especially in older patients. Moreover, the incidence and prevalence of AF is higher in patients with malignancy compared to general population, either at the time of cancer diagnosis or during the course of the disease[3]. This may be a result of comorbid conditions (such as hyper-

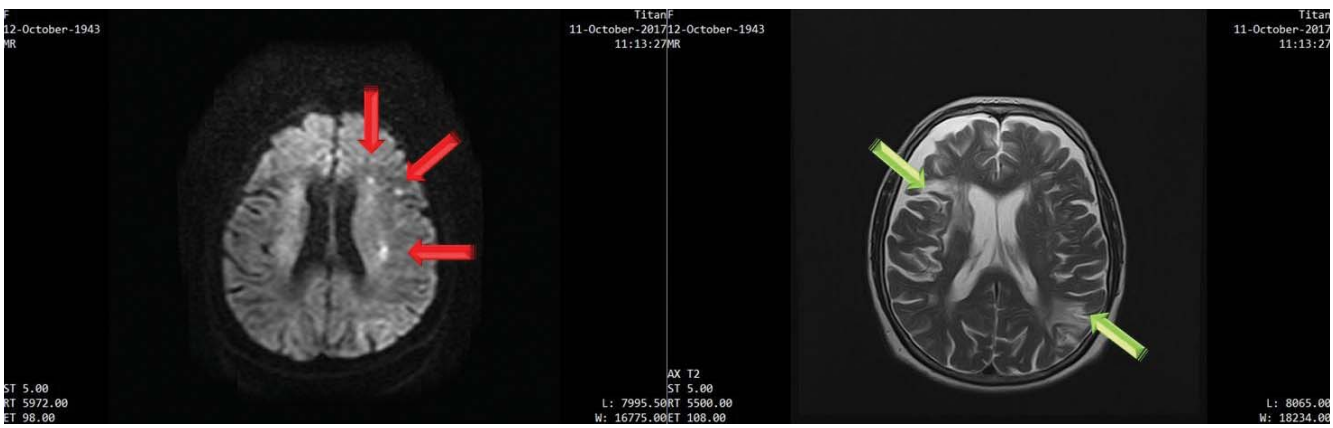

Figure 1. Brain computed tomography image showing multiple chronic sequelae (green arrows), with no recent lesions and no haemorrhage.

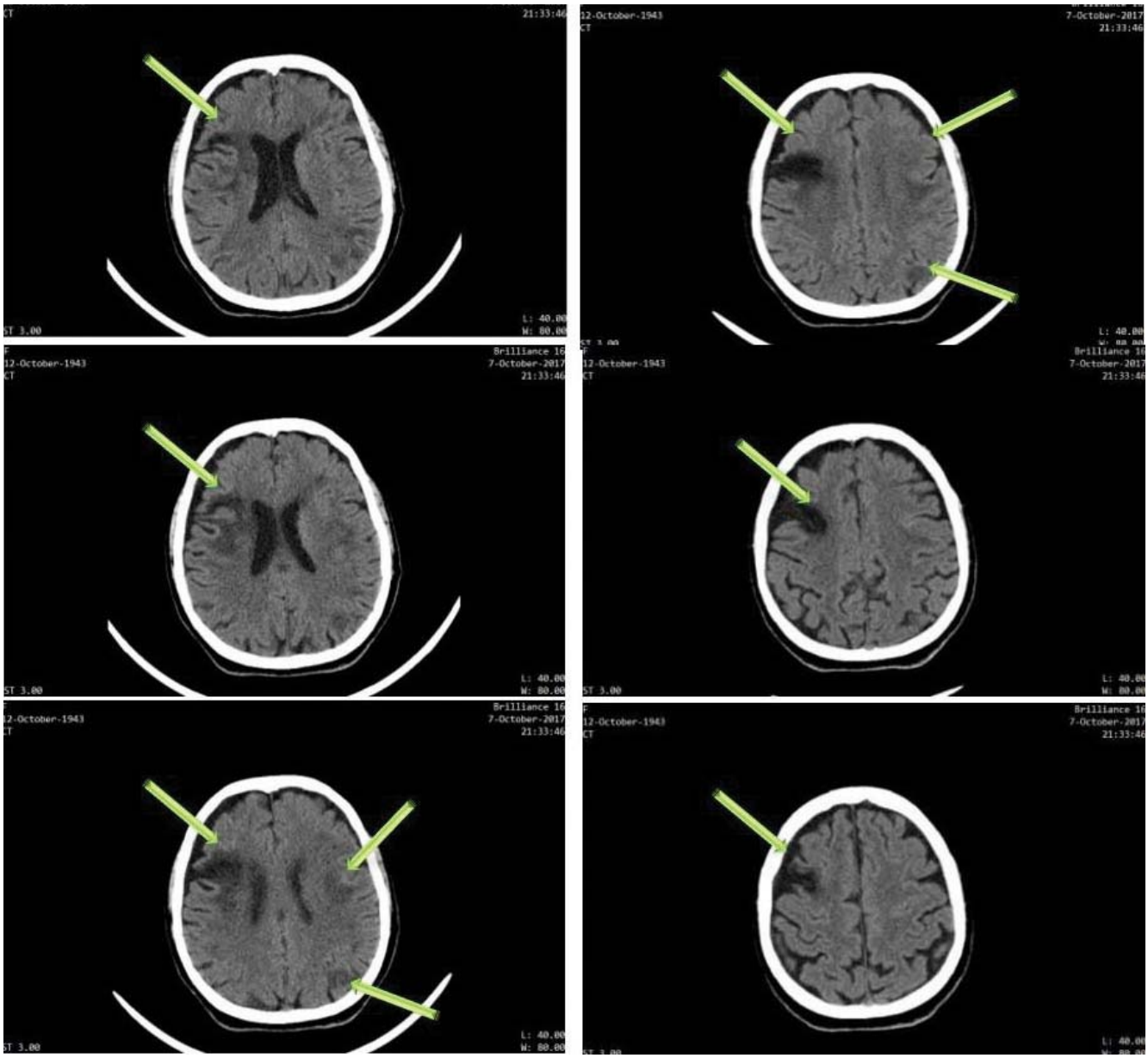

Figure 2. Diffusion magnetic resonance imaging revealing three acute ischemic lesions (red arrows) in multiple vascular territories and chronic lesions (green arrows).

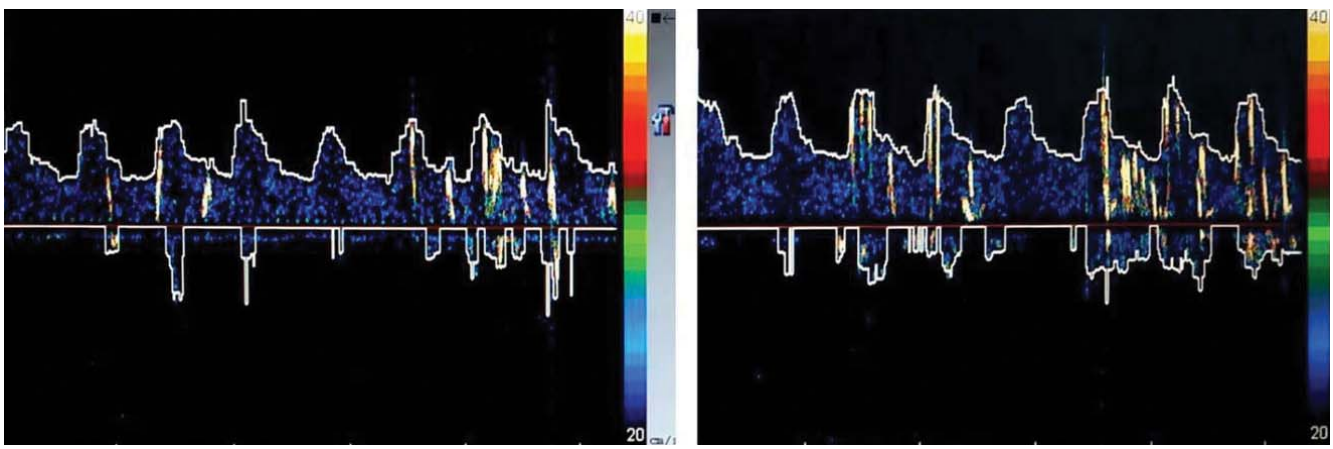

Figure 3. Transcranial Doppler image showing frequent bilateral microembolic signals.

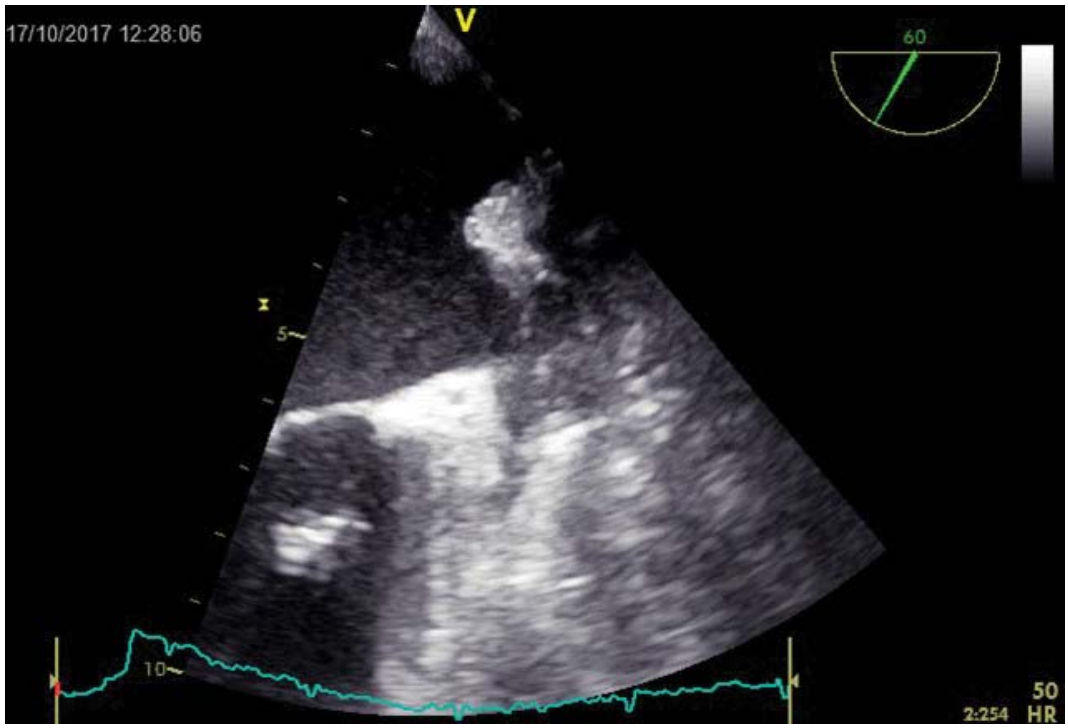

Figure 4. Transoesophageal echocardiography image showing left atrial appendage thrombosis.

tension), direct tumour effect (systemic inflammation, dehydration), as a complication of cancer therapy, or due to increased survival in cancer patients[3]. Both age and malignancy increase the risk of thromboembolic events as well as the risk of bleeding[4]. Hence, anticoagulation therapy in cancer patients is challenging.

In our case, the patient was diagnosed with recurrent ischemic cardioembolic stroke in the context of atrial fibrillation and left atrial appendage thrombus, requiring long term anticoagulation. There are currently no clear guidelines for anticoagulant therapy in patients with cancer and stroke. The most recent recommendations emphasize the importance of interdisciplinary teamwork to estimate individual patient risk and choose the most appropriate therapy, also considering patient preference[3]. Low molecular weight heparin (LMWH) is contraindicated in secondary prevention in the setting of acute stroke, but may be an option for long-term treatment[3]. Vitamin K antagonists (VKAs) were traditionally preferred over DOACs in cancer patients, based on greater clinical experience with these drugs[3]. However, difficulties in achieving a good anticoagulation control, most frequently with supratherapeutic levels of INR, increase the general concern of bleeding risk[5]. Localized bleeding diathesis as a result of local injury by tumour invasion, tissue damage from radiation, mucosal bleeding from visceral malignancies or thrombocytopenia from myelosuppressive chemotherapy can also increase the risk of bleeding[5].

Additionally, our patient presented with mild anemia, but refused any further invasive diagnostic tests. However, this condition proved to be chronic and there were no recent signs of active bleeding. Moreover, the small cerebral lesions diagnosed by diffusion MRI are associated with a low risk of haemorrhagic transformation, and allow for anticoagulation treatment initiation three days from the acute stroke onset.

Several characteristics may support the use of DOACs as a reasonable choice in cancer patients with AF for long-term treatment: shorter half-life compared to VKAs (which may be an important issue for interruptions in case of invasive procedures), lower intracranial bleeding risk, less food or drug interactions, easier administration and no need for INR control.

Active malignancy was an exclusion criteria in most DOAC AF trials[3]. An exploratory analysis in the ARISTOTLE trial of AF patients and active or a history of cancer showed the superior safety and efficacy with apixaban versus warfarin among patients with and without cancer[6]. Apixaban was associated with a greater benefit for the composite of stroke/systemic embolism, myocardial infarction and death in active cancer (HR 0.30, 95% CI 0.11-0.83) versus without cancer (HR 0.86, 95% CI 0.78- 0.95)[6].

CONCLUSION

The choice of anticoagulation therapy in cancer patients with atrial fibrillation and stroke remains challenging. The underlying malignancy is associated with a higher risk both for bleeding and prothrombotic state. DOACs may be a reasonable choice in this category of patients, however further randomised controlled trials need to address the multiple treatment choices we have.

Conflict of interest: none declared.

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