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Recurrent paraneoplastic cerebral hemorrhage in lung cancer: A case report

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Abstract:

Cerebral hemorrhage management in a patient requiring anticoagulant therapy is a therapeutic challenge also due to the absence of guidelines that convincingly define the best therapeutic strategy. Although the occurrence of cerebral hemorrhage in a patient with anticoagulant therapy seems to make the bleeding etiology obvious, sometimes, it is better to reflect on other possible causes and set up an adequate diagnostic workup. Herein, we describe a case of a 73-year-old male patient with atrial fibrillation, mechanical heart valve, and pacemaker that experienced an ischemic minor stroke during steady anticoagulation therapy with recurrent intracerebral haemorrhages (ICHs).

Keywords:

Anticoagulation, cancer, hemorrhage, intracerebral hemorrhages, neoplasm, prosthetic valve

Introduction

Atrial fibrillation in a patient bearer of mechanical prosthetic heart valves requires lifelong anticoagulation with Vitamin K antagonists (VKAs). The international normalized ratio (INR) should be kept among 2.5 and 3.5[1] even if this is significantly associated with an increased risk of major bleeding. The occurrence of ischemic stroke in these patients requires temporary anticoagulant discontinuation in large strokes, due to hemorrhagic infarction high risk. On the other hand, the reintroduction of anticoagulants must be as timely as possible due to the high risk of thromboembolism and restroke. The clinical balance between ischemic and hemorrhagic risk is a complex therapeutic challenge. Indeed, other factors, such as hypertension, elderly age, amyloid angiopathy, and cancer, may result in an imbalance in favor of hemorrhagic risk.[2,3] Herein, we describe the case of a patient with a mechanical valve and a long history of anticoagulation therapy that experienced an ischemic stroke followed by recurrent intracerebral hemorrhages (ICHs).

Case Report

A 73-year-old patient, a former smoker, with atrial fibrillation and bearer of mechanical aortic valve and pacemaker for about 20 years, was admitted to the emergency department (ED) for acute onset of face drooping and dysarthria. His medical history was remarkable for rheumatic heart disease, dilated cardiomyopathy, and chronic atrial fibrillation under treatment with amiodarone, beta-blockers, and warfarin. Tests on admission showed INR = 2.29 and therefore he could not be eligible for systemic thrombolysis.[4-6] Brain computed tomography (CT) scan with CT angiography with contrast was performed in ED but did not reveal acute ischemic or hemorrhagic lesions nor large vessel

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occlusions. The patient was admitted to the stroke unit for diagnostic workup. CT brain performed at 24 h from symptoms onset showed a small right frontal hypodense (<15 mm) lesion.

During hospitalization, transesophageal echocardiography showed auricular thrombosis with a severely left atrial enlargement, without any evidence of acute endocarditis. Because to the high risk of ischemic stroke recurrence in a patient with mechanical heart valve, atrial fibrillation, and auricular, warfarin prompt reintroduction was critical. Therefore, warfarin was reintroduced after 3 days[7] and INR was monitored.

He could not perform an MRI brain due to pacemaker incompatibility, thus after 5 days from admission to the stroke unit, a control brain CT scan [Figure 1a] was repeated and showed two acute spontaneous hemorrhagic areas in the right frontal lobe without clinically evident neurological deficits with INR = 2.9. Anticoagulation was immediately stopped.

Clinical suspicion was hemorrhagic infarction of ischemic stroke due to early anticoagulant therapy reintroduction. Decision has been taken: To evaluate the bleeding progress and to reinstate anticoagulant only after stabilization of the CT brain imaging. After 2 weeks from symptoms onset, CT brain follow-up showed stability and regression of hemorrhagic findings. Anticoagulant therapy has been reintroduced with low-molecular-weight heparins and later with warfarin due to the stability of CT brain lesions [Figure 1b]. Unfortunately, 5 days after warfarin reintroduction (17 days after stroke unit admission), the patient complained of an acute onset of dizziness and left arm weakness, the new brain CT scan showed nontraumatic hemorrhagic spot in the paramedian right subcortical area [Figure 1c] and tests showed an INR = 3.4. Anticoagulation was again stopped. For intolerance to anticoagulant therapy associated with major INR fluctuations in a patient with a very high thromboembolic risk, collegial assessment with the cardiologist and cardiac surgeon was made, and it was suggested to replace the mechanical aortic valve and to close the left atrial appendage after stabilization of the neurological deficit. This approach, indeed, allows us to stopped anticoagulation and reduced both the hemorrhagic and ischemic stroke risk.

A new brain CT scan was performed after 72 h from the last one [Figure 1d] and showed the evolution of right frontal and right paramedian subcortical hemorrhagic spots.

Location, morphological features, and evolution of the lesions with the sudden tendency to bleed, in a patient who had been using warfarin for 20 years without severe INR fluctuations (2.29 to 3.4) and history of previous hemorrhages needed the evaluation of other causes for ICHs.[2,3]

Concurrent presence of ischemic stroke and recurrent spontaneous cerebral bleeding in a regular smoker, after ruling out vascular malformations, amyloid angiopathy, and head trauma, led to the suspicion of a paraneoplastic syndrome. A total body CT scan with contrast performed in 22nd day showed a nodular formation with contrast enhancement in the superior

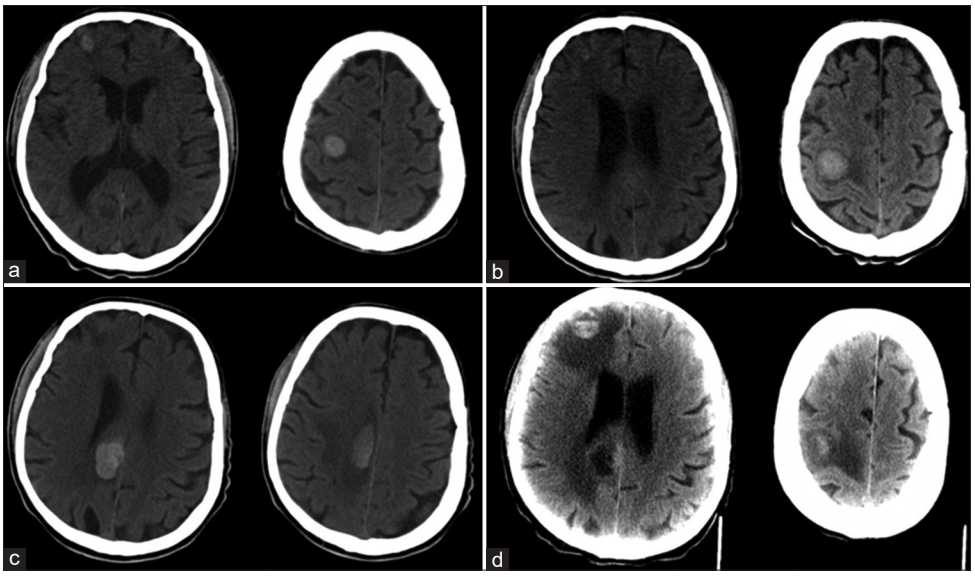

Figure 1: CT images showing the evolution of the hemorrhagic picture. The first two hemorrhagic spots in the right frontal site (a), and the evolution of the lesion after 5 days (b). After 10 days, a new right subcortical paramedian hemorrhage appears (c). The last two hemorrhages at the same site as the first lesion. It is possible to note the presence of a fluid level in the context of the frontal lesion (d). CT: Computed tomography

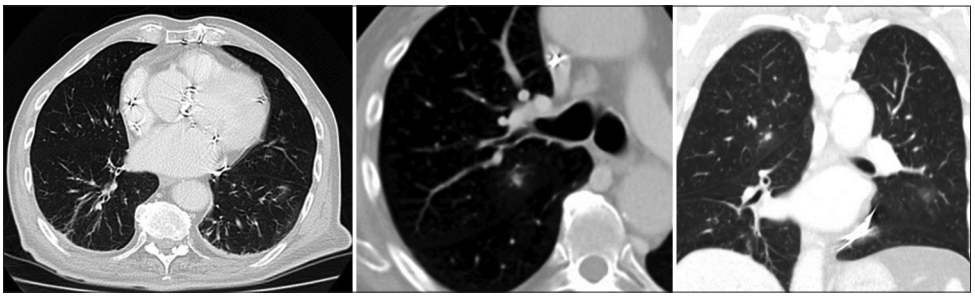

Figure 2: Solid nodular formation (about 8 mm) with irregular margins and faded increase in surrounding parenchymal density in the dorsal segment of the right upper lobe; adjacent, minute nodule with the same densitometric characteristics

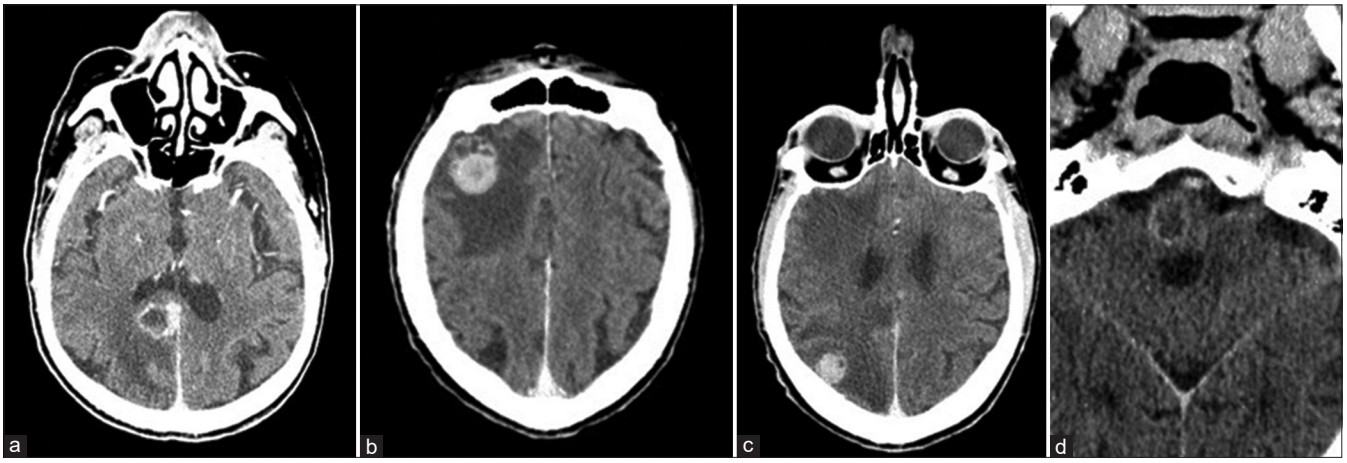

Figure 3: Nodular formation in periventricular posterior paramedian level (a), frontal lobe (b), occipital lobe (c), and pons. In particular (a and d) show peripheral contrast uptake with hypodense core

lobe of the right lung [Figure 2]. Brain sequences showed new hemorrhagic lesions in the right frontal and occipital lobes and multiple small postcontrast enhancing lesions in the brain suggestive of lung cancer metastasis [Figure 3a-d].

In our patient, the paraneoplastic syndrome due to lung cancer caused a pro-ischemic state that leads to an ischemic stroke. At the same time, there was a prohemorrhagic state with recurrent cerebral hemorrhages due to cerebral metastases.

The patient died 2 weeks after the diagnosis of metastatic lung cancer from a severe urinary tract infection that did not respond to antibiotic therapy and was complicated by septic shock with cardiac arrest. An autopsy was refused by the family without being able to characterize the type of lung cancer.

Discussion

Italian, European, and American guidelines do not provide adequate information on how to manage the use of anticoagulant therapy in complex patients.[4-6]

There are still no well-characterized algorithms on the timing of anticoagulant resumption in patients with acute intracranial hemorrhage and indications for the use of anticoagulant therapies.[7] Most studies have shown that oral anticoagulant resumption does not increase the risk of recurrent ICH.[8-12] Nevertheless, other studies show an increased bleeding rate in patients in whom anticoagulant has been reinstitute.[13,14] Therefore, it is suggested that the risk profile should be evaluated on a patient-by-patient basis when deciding whether to reintroduce anticoagulant therapy and on the timing of resumption.[15]

In our case, there were several risk factors for thromboembolic events and the patient had been on anticoagulant therapy for more than 20 years without significant adverse events.

He presented an abrupt change in response to anticoagulant therapy that may raise questions about other causes of stroke.

Approximately 15% of cancer patients have a stroke that may either follow or precede the diagnosis.[16] A coagulation disorder, commonly found in oncology patients, may lead to ischemic/hemorrhagic strokes that are more common in smoking-related cancers (i.e. lung, colon, bladder, etc.).[17] Cerebrovascular disease significantly impacts on prognosis in this population

and management is extremely delicate. Actually, both VKAs and direct oral anticoagulants appear to be safe and efficacious for stroke prevention in patients with cancer.[18] In our patient, we necessarily used VKAs but we evaluated the replacement of the mechanical valve with a biological prosthesis and the left appendage closure, thus eliminating the need to long-term anticoagulation. However, his cancer was extremely aggressive and he died before cardiac surgery.

Unfortunately, guidelines are not comprehensive and in this kind of clinical scenario do not help to make the best therapeutic choice.

Conclusion

There are two crucial points in this case report: management of anticoagulation therapy in real patients with multiple comorbidities and risk factors and to keep an open mind and not to stopping to the most obvious conclusion.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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