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Recurrent Ischemic Stroke Despite Therapeutic Anticoagulation: Evidence of Dual Embolic Mechanisms

—Running Head: Breakthrough Stroke with Dual Embolic Origin

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Abstract

Background: Ischemic stroke occurring despite effective oral anticoagulation, termed "breakthrough stroke," represents a diagnostic and therapeutic challenge. It may indicate the presence of alternative or concomitant etiological mechanisms beyond the initially identified cause. Data regarding such situations remain limited in sub-Saharan Africa. We report a case of recurrent ischemic stroke despite therapeutic anticoagulation, revealing a dual embolic origin. **Methods and Findings:** A 50-year-old right-handed woman with poorly controlled hypertension was admitted for sudden onset left-sided hemiparesis (NIHSS score 13). Non-contrast brain CT scan showed a hypodensity in the territory of the right middle cerebral artery. Electrocardiogram revealed atrial fibrillation. Anticoagulation was initiated with enoxaparin followed by fluindione, achieving a therapeutic INR of 2.3. Initial evolution was favorable, with motor improvement at day 14 (NIHSS score 6). Three weeks later, the patient was readmitted for worsening neurological deficit despite good treatment adherence (INR 2.05). Follow-up CT scan showed extension of the infarction in the same vascular territory. Further etiological evaluation with Doppler ultrasound revealed significant right internal carotid artery stenosis with an unstable, ulcerated plaque. The coexistence of atrial fibrillation and carotid atherosclerosis suggested a dual embolic mechanism. The clinical course was unfavorable, with progressive neurological deterioration leading to

death. **Conclusions:** This case illustrates the complexity of etiological reasoning in ischemic stroke. Stroke occurring despite adequate anticoagulation should prompt systematic reassessment for alternative or additional embolic mechanisms. In resource-limited settings, comprehensive etiological evaluation remains a major challenge requiring a pragmatic and individualized approach.

Keywords

Ischemic Stroke, Atrial Fibrillation, Breakthrough Stroke, Carotid Atherosclerosis, Dual Embolic Mechanism, Anticoagulation, Sub-Saharan Africa

1. Introduction

Ischemic stroke represents the most common form of stroke, with a predominance of embolic mechanisms [1]. Among these, atrial fibrillation is a major cause of cardioembolic stroke, exposing patients to a high risk of recurrence in the absence of anticoagulation [2] [3]. In parallel, carotid atherosclerosis remains an important etiology, particularly in the presence of unstable plaques with high embolic potential [4]. Secondary prevention relies primarily on identifying the underlying mechanism and initiating appropriate treatment. However, the occurrence of ischemic stroke despite effective anticoagulation, referred to as "breakthrough stroke," poses a diagnostic and therapeutic challenge, suggesting the possible existence of concomitant etiological mechanisms [5].

Data regarding such situations remain limited in sub-Saharan Africa, where restricted access to diagnostic tools and modern therapies may influence clinical reasoning and patient management. To our knowledge, no similar case has been reported in Togo to date.

We report the case of a patient who experienced a recurrence of ischemic stroke despite effective anticoagulation, revealing a dual embolic origin.

2. Case Presentation

A 50-year-old right-handed woman, a trader, was admitted for sudden onset left-sided hemiparesis. Her medical history included poorly controlled hypertension and a sedentary lifestyle related to her occupation. She had been menopausal for three years. There was no known history of cardiovascular disease. She was admitted 48 hours after symptom onset. On examination, blood pressure was 185/100 mmHg in the right arm and 190/110 mmHg in the left arm. Temperature was 37.3˚C, oxygen saturation was 97% on room air, and body mass index was 31.4 kg/m^2. Neurological examination revealed a conscious and alert patient with dysarthria. Motor examination showed left hemiparesis, predominantly brachiofacial, graded 2/5 in the upper limb and 3/5 in the lower limb according to the Medical Research Council (MRC) scale, associated with left central facial palsy. Muscle tone and

deep tendon reflexes were decreased on the left side. The plantar response was indifferent on the left and normal on the right. There was left-sided hypoesthesia to touch and temperature. Cranial nerve examination, coordination, and meningeal signs were unremarkable. The National Institutes of Health Stroke Scale (NIHSS) score at admission was 13. Cardiovascular examination revealed an irregularly irregular rhythm without murmurs or signs of heart failure. Non-contrast brain computed tomography (CT) scan showed a hypodensity in the territory of the deep branches of the right middle cerebral artery (**Figure 1(A)**). Initial laboratory tests were unremarkable. Electrocardiogram revealed atrial fibrillation, while transthoracic echocardiography showed no left ventricular thrombus, valvular disease, or major structural abnormality. A diagnosis of cardioembolic ischemic stroke was initially retained. Anticoagulation therapy was initiated on the day of admission with prophylactic-dose enoxaparin after non-contrast CT had confirmed an ischemic stroke. Following the diagnosis of atrial fibrillation, enoxaparin was escalated to therapeutic dose and fluindione was initiated simultaneously. Both treatments overlapped for six days until the INR reached the therapeutic range (target 2.0 - 3.0). INR was monitored every 48 hours following dose adjustments. Before discharge, the INR had stabilized at 2.3, after which fluindione was continued alone. Antihypertensive therapy and proton pump inhibitor prophylaxis were also prescribed. Early rehabilitation was initiated. Initial evolution was favorable, with motor improvement to 4/5 strength at day 14 (NIHSS score 6), and the patient was discharged home.

Three weeks later, she was readmitted for worsening neurological deficit despite good treatment adherence. The last INR before admission was 2.05. Follow-up CT scan showed extension of the infarction in the same vascular territory (**Figure 1(B)**). The clinical presentation was consistent with a recurrent embolic event rather than mere progression of the initial infarct, as the patient had demonstrated sustained clinical improvement over two weeks (NIHSS from 13 to 6) with stable therapeutic anticoagulation before the abrupt worsening occurred after a three-week symptom-free interval. Follow-up CT scan excluded hemorrhagic transformation. Biological findings remained unchanged, with no evidence of infection, dehydration, or metabolic disturbance. Blood pressure at readmission was comparable to previous values. Given the recurrence under effective anticoagulation, further etiological evaluation was performed. Doppler ultrasound of supra-aortic vessels revealed significant right internal carotid artery stenosis, estimated at 73% according to NASCET criteria, associated with an ulcerated, mobile (floating) plaque classified as unstable based on surface irregularity and intraluminal protrusion. Carotid atherosclerosis was considered the most likely cause of recurrence, suggesting an artery-to-artery embolic mechanism and highlighting the possibility of dual etiology. Antiplatelet therapy was not initiated due to the high risk of hemorrhagic transformation associated with the large infarct volume. Carotid revascularization by endarterectomy or stenting was not feasible, as these procedures are not available in our setting. Switching to a direct oral anticoagulant

was not possible given limited local availability and affordability. The clinical course was unfavorable, with progressive neurological deterioration and impaired consciousness, leading to death.

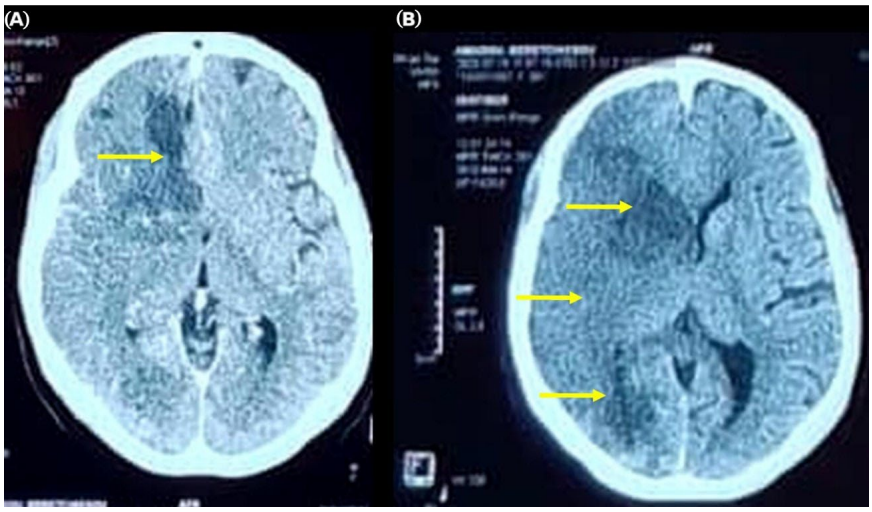

Figure 1. Non-contrast axial brain CT scan showing ischemic infarct in the right middle cerebral artery territory. (A) Initial CT scan at admission: axial slice at the level of the lateral ventricles demonstrating a hypodensity involving branches of the right middle cerebral artery (arrow), consistent with an established ischemic infarct. (B) Follow-up CT scan three weeks later: axial slice at the same anatomical level showing extension of the hypodensity in the same vascular territory (arrow), despite therapeutic anticoagulation (INR 2.05).

3. Discussion

This report describes the case of a 50-year-old patient who presented with an ischemic stroke initially attributed to atrial fibrillation, based on the identification of a rhythm disorder on electrocardiography. The initial course under effective anticoagulation, with documented therapeutic INR levels, was favorable, before the occurrence of an early recurrence in the same vascular territory. However, the occurrence of recurrence in the same territory despite adequate anticoagulation (INR = 2.05) represents a key element suggesting an alternative or associated etiology. This situation is typical of a "breakthrough stroke," as described by Seiffge DJ *et al.* and other authors [1]-[3]. This case thus illustrates the limitations of a univocal etiological reasoning in ischemic stroke and highlights the possibility of a dual embolic origin, both cardioembolic and arterial, as reported notably by Ay H *et al.* [4] and Arsava EM *et al.* [5].

Ischemic stroke accounts for approximately 80 to 85% of all strokes worldwide [6]. Atrial fibrillation represents one of the main causes of cardioembolic stroke, being involved in nearly 20% to 30% of cases [7] [8]. Its incidence increases with age and associated cardiovascular risk factors, particularly hypertension [9], which was also present in our patient. In parallel, carotid atherosclerosis accounts for approximately 10% to 20% of ischemic strokes, as reported by Naylor AR *et al.* [10]. Unstable plaques, particularly those with ulcerations or thrombotic

changes, are associated with a high risk of artery-to-artery embolization [11] [12]. In this context, either a cardioembolic or an arterial origin may explain the occurrence of ischemic stroke. However, the difficulty in definitively attributing a single cause in our case led to the hypothesis of an etiological coexistence. Indeed, the coexistence of multiple etiological mechanisms is not uncommon. Ay H *et al.* reported, in 2005, that approximately 13% of patients presented multiple embolic sources [4], while Arsava EM *et al.* reported a frequency of around 12% to 15% in 2010 [5]. This situation is particularly frequent in patients with multiple vascular risk factors, as in our patient. Regarding breakthrough strokes, their incidence in patients under effective anticoagulation is estimated at 1% to 2% per year [2] [13]. These events are often associated with alternative or concomitant causes not identified during the initial evaluation, as reported notably by Polymeris AA *et al.* [2] and Seiffge DJ *et al.* [3].

The pathophysiological mechanisms of the two etiologies considered are distinct and well established. Atrial fibrillation promotes the formation of intra-atrial thrombi, particularly in the left atrial appendage, due to blood stasis and impaired contractile function, as initially demonstrated by Blackshear JL, Odell JA *et al.* [14]. This central role of the left atrial appendage in the genesis of embolism has been confirmed by more recent studies, notably those by Khurram IM *et al.* [15] and Sulague RM *et al.* [16]. These thrombi may subsequently embolize to the cerebral circulation, leading to large infarcts, often cortico-subcortical [17].

Cardioembolic ischemic strokes are frequently multiterritorial, either during the same episode or at recurrence, as described by Kimura K *et al.* [17], as well as by more recent studies such as those by Ntaios G *et al.* [18] and Veltkamp R *et al.* [19]. However, effective anticoagulation significantly reduces the embolic risk without completely eliminating it [20]. Thus, the occurrence of stroke under anticoagulation requires consideration of several hypotheses, including poor adherence, insufficient anticoagulation, or the presence of an alternative etiological mechanism [21] [22]. In our case, the therapeutic INR and good adherence made treatment failure unlikely. Furthermore, the recurrence in the same vascular territory supported a local mechanism rather than a diffuse cardioembolic origin.

The secondary identification of an unstable and ulcerated carotid plaque supported an artery-to-artery embolic mechanism. Vulnerable plaques are characterized by fibrous cap rupture, exposure of the lipid core, and the formation of a mural thrombus, promoting distal embolization [23] [24]. Unlike emboli of cardiac origin, which are often multiple and variably distributed, carotid emboli tend to recur in the same cerebral territory [24] [25]. This case therefore illustrates a situation of dual embolic mechanism, in which atrial fibrillation and carotid plaque may both contribute, in a non-exclusive manner, to the occurrence of ischemic stroke [1] [18].

The management of cardioembolic stroke is primarily based on oral anticoagulation, which significantly reduces the risk of recurrence [26]. Vitamin K antagonists, such as fluindione, remain widely used in certain settings, although direct

oral anticoagulants are currently preferred in most international guidelines, particularly those of January CT *et al.* [26]. In resource-limited settings, the use of vitamin K antagonists is often dictated by financial constraints, as direct oral anticoagulants remain costly and less accessible. This reality significantly influences therapeutic strategies, as reported in studies conducted in sub-Saharan Africa, notably by Owolabi MO *et al.* in 2018 [27].

In the presence of symptomatic carotid stenosis, particularly when associated with an unstable or ulcerated plaque, carotid revascularization, either by endarterectomy or stenting, may be indicated, especially when the degree of stenosis exceeds 70%, as demonstrated in landmark trials such as NASCET and ECST [28] [29]. The benefit of this intervention is greater when performed early after the ischemic event, as demonstrated by Rothwell PM *et al.* [30], and confirmed by Azhar *et al.* in 2020 [31] and Chisci *et al.* in 2022 [32]. The coexistence of an indication for anticoagulation and significant carotid disease represents a true therapeutic challenge. The combination of anticoagulant and antiplatelet therapy is not systematic, due to the increased risk of bleeding, and should be considered on a case-by-case basis according to the patient's risk profile, as highlighted in recent recommendations, notably those of Joglar JA *et al.* [33], as well as studies by Martini L *et al.* [34].

The prognosis of stroke depends on several factors, including initial severity, etiology, and timeliness of management. Cardioembolic strokes are generally associated with a more severe prognosis due to the size of infarcts. Early recurrence is a factor of poor prognosis, increasing the risk of disability and mortality [35]. In our case, recurrence despite effective anticoagulation highlights the need for increased vigilance.

This case has several limitations inherent to the diagnostic workup available in our setting. Brain MRI, CT angiography, and transesophageal echocardiography were not performed, limiting further characterization of the embolic sources, including a more precise assessment of infarct extent, plaque morphology, and potential intracardiac sources such as left atrial appendage thrombus. These limitations should be considered when interpreting the proposed dual embolic mechanism, and they underscore the diagnostic challenges encountered in resource-limited environments.

4. Conclusions

This case highlights the complexity of etiological reasoning in ischemic stroke, particularly in patients with multiple risk factors. Stroke occurring despite adequate anticoagulation should prompt consideration of alternative or additional mechanisms.

It emphasizes the importance of comprehensive etiological assessment and systematic reassessment in cases of atypical evolution. In resource-limited settings, these situations represent a major challenge requiring a pragmatic and individualized approach.

Ethical Statement

Written informed consent for publication of this case report and accompanying images was obtained from the patient's next of kin. This case report did not require formal ethics committee approval as per institutional policy for retrospective single-case observations.

Author Contributions

LA conceived the case report, collected the clinical data, and wrote the original manuscript. KMG and NKA contributed to clinical management and critically reviewed the manuscript. AEG and KA contributed to the diagnostic workup and data collection. VKK and DK participated in the clinical follow-up and contributed to the literature review. KAs, BM, and AAB supervised the study, critically revised the manuscript, and approved the final version. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

BMI	Body Mass Index
CT	Computed Tomography
ECST	European Carotid Surgery Trial
INR	International Normalized Ratio
MRC	Medical Research Council
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institutes of Health Stroke Scale
DOAC	Direct Oral Anticoagulant