Case report

Failure of non-vitamin K antagonist oral anticoagulants in preventing stroke in elderly patient: a case report of multiple strokes on standard of care treatment for atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common type of treated heart arrhythmia. Generally, the treatment goals for atrial fibrillation are to reset the rhythm or control the rate and prevent the development and subsequent embolization of atrial thrombi. These thromboembolic events can occur with any kind of atrial fibrillation that is paroxysmal, persistent or permanent. In patients who are candidate for anticoagulation therapy, major practice guideline provides vitamin K antagonist (VKA) oral anticoagulant and non-VKA oral anticoagulants as treatment options. The risk of AF increases with age and despite treatment on standard of care anticoagulation therapy, recrudescent cardioembolic events may still arise especially in the elderly as we will see in this case.

Keywords: *atrial fibrillation; oral anticoagulation; stroke*

Introduction

A study by Kato et al. suggests that in the currently aging society (albeit in Japan), cardioembolic stroke is the most important stroke subtype [1]. According to that study, the role of hypertension, diabetes mellitus, and hyperlipidemia are greatest in stroke patients in their 50s and 60s while in older patients, the role of atrial fibrillation (AF) is more significant.

AF is associated with a 50% to 90% increase in all cause of mortality particularly from the increased risk of cardiovascular death including stroke [2]. The elderly in particular have increased risk of stroke with AF. The incidence of stroke and the prevalence of AF increase with age [3].

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Major advances have been made in the management of AF. Despite these advances, substantial morbidity and mortality remains. Oral anticoagulation (OAC) with vitamin K antagonists (VKA) or non-VKA oral anticoagulation (NOAC) markedly reduces stroke and mortality in AF patients and have become the cornerstone of treatment to reduce the risk of cardioembolic events (class recommendation I, level of evidence A) [4-7].

However, as noted in the case below, the use of oral anticoagulants remains suboptimal in elderly patients with AF [6].

Case presentation

We present the case of an 84-year-old left-handed, white female, nonsmoker, nonalcoholic, who presented to the emergency department (ED) on 09/23/19 in the early evening shortly after experiencing dysarthria and transient left-hand tremor (around 18:30) concerning for an acute stroke. She was not a

candidate for Alteplase (tPA) due to recent stroke and current use of apixaban.

She has a history of hypertension, non-insulin dependent diabetes mellitus, atrial fibrillation diagnosed in 2017 (paroxysmal AF with spontaneous reversal at the time of diagnosis and which was initially treated with 2.5 mg of apixaban twice daily) with 1 prior cardiovascular accident (CVA) in the left frontotemporal infarction seen on MRI on 08/09/2019, no tPA was administered.

Earlier that evening prior to arriving to the ED, the patient was eating dinner and abruptly noticed that she had tonic jerky movements of her left hand which she could not control. The episode lasted a few minutes. Subsequently, she noticed right facial droop, slurred speech and expressive aphasia. She denied diplopia or difficulty swallowing. She denied weakness in her extremities. She endorses previous history of abrupt onset expressive aphasia which lasted 3-4 days or so during the CVA on 08/09/2019 (positive on MRI as stated above). She was on apixaban 2.5 mg twice a day (BID) by mouth (p.o.) at the time which was increased to 5.0 mg BID p.o. upon discharge. Physical examination was grossly unremarkable other than noted left corner of the mouth facial droop and slurred speech per the admitting physician. NIHSS stroke scale was 2.

Admission imaging and diagnostic results. In the ED, an electrocardiogram (EKG) revealed sinus rhythm with heart rate of 89 beats per minutes, right bundle branch block, T wave inversions in inferior leads and poor R-wave progression as read by the cardiologist. The report of the brain computed tomography (CT) without contrast obtained at 19:33 showed no acute intracranial hemorrhage, midline shift or mass effect but revealed age indeterminate infarct in the left frontal lobe per the reading radiologist. CT angiography performed at 19:51 reported no focal flow-limiting stenosis, occlusion or aneurysm involving the anterior and posterior circulation of the brain nor any hemodynamically significant stenosis or occlusion involving the major arterial vessels of the neck. Brain MRI (Figures 1 and 2) performed at 22:05 revealed subacute infarct in the left frontal lobe at the gray-white matter junction. There was an acute infarct involving the right frontotemporal cortex just above the right sylvian fissure and chronic ischemic changes and cortical atrophy. An echocardiogram performed on 09/23/2019 at 21:54 reported an ejection fraction estimated at 60-65% with grade I diastolic dysfunction and no gross regional wall motion abnormalities. There was aortic valve calcification without hemodynamically significant stenosis.

Laboratory findings were grossly unremarkable: white blood cell (WBC)=7.1 10*3/uL, hemoglobin (Hb)=13.0 g/dL, hematocrit (Hct)=38.3%, platelets (PLT)=250 10*3/uL, prothrombin time (PT)=13.1 seconds (secs), activated partial thromboplastin time (aPTT)=30.6 secs, INR=1.0. Myocardial enzymes (troponins I) were unremarkable (<0.015, <0.015, <0.015). Electrolytes were grossly unremarkable. Blood urea nitrogen (BUN)=22 mg/dL, Creatinine=1.260 mg/dL. Glucose=228 mg/dL. Hepatocytolysis enzymes were grossly unremarkable (AST 35, ALT 83, Alkaline phosphatase 103). She was administered 324 mg of aspirin orally and admitted for further evaluation.

Regarding clinical and pharmacological history at the time of this current presentation, for anticoagulation due to her history of AF, she was on apixaban 5 mg p.o. daily (qd). For rate control, she was reportedly on oral diltiazem 120 mg daily and for rhythm control, oral sotalol 80 mg BID. In addition, the patient was on rosuvastatin 20 mg daily qd p.o for cardiovascular event prevention and metoprolol succinate 25 mg qd p.o. for hypertension. Canaglifozin 300 mg p.o. daily and sitagliptin 100 mg p.o. daily for diabetes. Levothyroxine 88 mcg p.o. daily for hypothyroidism. For the past month prior to this ED visit, she had been complaining of headaches localized over the forehead, more so on the left side, off and on. She has history of chronic headaches in the past and was diagnosed to have temporal arteritis. She was followed by a rheumatologist and treated with oral methotrexate 2.5 mg daily and 12.5 mg once a week on Thursdays as well as oral prednisone 2-3 mg a day. She suffers from major depressive disorder and was on oral paroxetine 20 mg once daily.

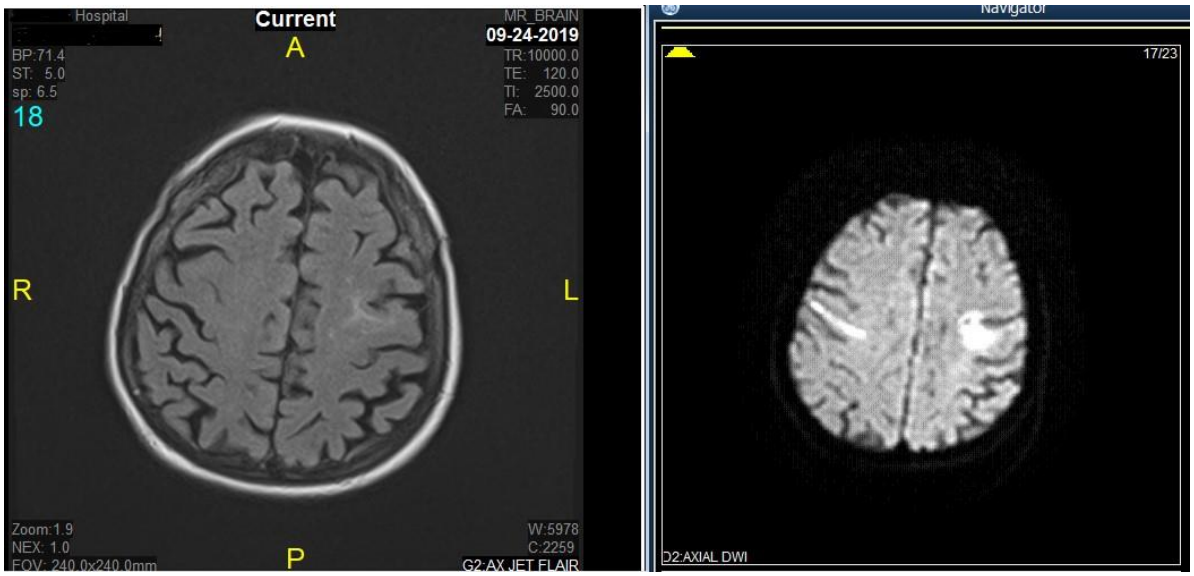

Fig. 1. MRI demonstrating subacute infarct in the left frontal lobe at the gray white matter junction

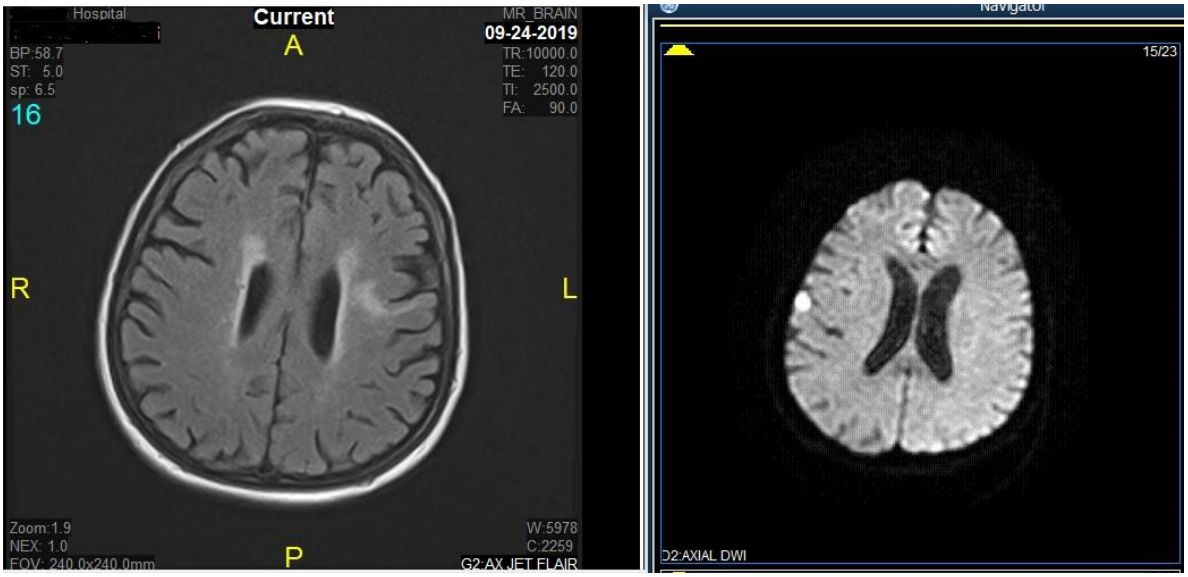

Fig. 2. MRI demonstrating an acute infarct involving the right frontotemporal cortex just above the right sylvian fissure

Upon admission, most of the aforementioned medications were withheld except for apixaban, metoprolol and paroxetine. Permissive hypertension was allowed for the first 24 hours. The patient's BP remained in systolic BP between 125-170 and diastolic between 55-77 during that timeframe. The patient was noted to have paroxysmal atrial fibrillation and was in sinus rhythm at the time of the encounter with the cardiologist around 21:59 on the day of admission. Metoprolol was discontinued by day 1 (09/24/2019) by the cardiologist after noticing heart rate sustaining in the 60s beats per minutes. Sotalol was resumed on day 1 and administered throughout her hospital stay. Lipid profile on 09/24/2019 revealed triglycerides of 81 mg/dL, cholesterol of 185 mg/dL, low density lipoprotein (LDL) of 94 mg/dL, high density lipoprotein (HDL) of 75 mg/dL. LDL goal was less than 70 mg/dL hence atorvastatin at a higher dose of 80 mg p.o. qd was started on day 1 and maintained throughout her hospital course. Levetiracetem was initiated at 1000 mg IV q12 hours upon admission due to possible right focal motor seizure involving her involuntary left hand clonic type activity. It was subsequently

reduced to 500 mg IV q 12 hours on day 4 and discontinued upon discharge due to no further seizure like activities. 2 mg of oral prednisone once daily was resumed on day 1 to continue management for her history of temporal arteritis as well as her daily levothyroxine and 81 mg of p.o. aspirin. Apixaban was discontinued on day 1 and she was bridged the same day to warfarin with heparin drip (discontinued on 10/02/2019). She was administered 5 mg p.o. daily of warfarin which was continued throughout the hospitalization with occasional administration of a 2.5 mg dose instead (on 10/01, 10/02 and 10/04) An INR goal of 2.0-2.5 was targeted and it remained between 1.0 to a peak of 2.3 on the day of discharge.

Repeat CT scan of the brain (on 09/27/19 and 10/02/19) were negative for hemorrhagic conversion or any other acute intracranial changes. She remained neurologically stable from the time of admission to the day of discharge on 10/06/2019. She was able to ambulate without assistance despite mild weakness in the left leg proximally and she remained in sinus rhythm on tele-monitoring throughout her hospital stay. Her dysarthria was very minimal prior to discharge with no significant changes in her facial weakness. She was recommended to continue to do facial exercises as well as physical and occupational therapy upon discharge. Apixaban, diltiazem, metoprolol, paroxetine and rosuvastatin were discontinued during this admission and rosuvastatin 40 mg p.o daily, warfarin 4 mg p.o daily, amlodipine 2.5 mg p.o daily, aspirin 81 mg p.o daily and vitamin B12 1000 mg p.o daily were added to her list of ambulatory meds. Medications for temporal arteritis, diabetes, hypothyroidism were renewed and for atrial fibrillation only sotalol was renewed.

Discussion

This case is about an 84-year-old female who presented with recurrent CVA most likely secondary to atrial fibrillation. Her 1st CVA was approximately 6 weeks prior to this admission while she was on apixaban 2.5 mg twice daily. The second event occurred while she was on apixaban 5.0 mg twice daily. She was discharged with the goal to transfer to acute rehab for further management. The patient would need intensive speech therapy.

Apixaban was shown via the ARISTOTLE trial to be superior to VKA in significantly reducing the primary end point of stroke in elderly patients by 21% [6]. This case clearly depicts failure of apixaban to prevent 2 CVAs. Despite the acuity of the recurrent stroke most likely cardioembolic in nature, neurology was not in favor of using thrombolytic therapy as she was not a good candidate. She had a stroke less than 3 months prior and was on chronic anticoagulation therapy with apixaban. Other sources of stroke were elucidated. Neurology recommended starting statins, checking SED rate, Hb A1c, B12, folate levels, thyroid and lipid profile. Echocardiogram and bubble study were indicated as well. Work up for hypercoagulable state was initiated as well.

There was suspicion for seizures secondary to embolic stroke hence an EEG was recommended as well but was not performed. Hemorrhagic stroke causing a seizure was ruled out as the CT scan of the brain was negative for an active bleed.

Management. She remained in sinus rhythm and her sotalol was continued as it appeared she was quite symptomatic when she was in atrial fibrillation. She was allowed to be in permissive hypertension upon admission however by the 2nd day of admission, her BP was uptrending and reached 160/75 mm Hg. Her metoprolol was held and she was continued on sotalol and added low-dose amlodipine for better pressure control. Her diabetes was managed with oral agents. Her facial droop persisted and her residual deficit did not improve significantly.

Hematology/oncology stated that in light of concerns that she was not adequately reducing her risk of embolic CVA on apixaban, she will be transitioned to warfarin with appropriate bridging anticoagulation. The rationale behind this switch was that her INR can be monitored closely and be adjusted if she is found to have another CVA with a therapeutic INR value.

Due to the patient's multiple autoimmune conditions, rheumatoid arthritis, temporal arteritis, and newly-diagnosed pernicious

anemia, there was suspicion of anti-phospholipid antibody syndrome. The following tests (Table 1) were ordered: anti-cardiolipin antibodies, beta-2 glycoprotein antibodies and lupus anticoagulant with the understanding that NOAC use can result in false-positive anticoagulant. Warfarin would be the preferred anticoagulant for a patient with these findings [8]. Repeating these tests after three months would be needed to prove persistent positivity in order to make the definitive diagnosis as these findings can be transient. Anti Xa level appears to be a more confounding marker to measure when trying to determine suspected failure to prevent ischemic stroke while on a NOAC such as apixaban (factor Xa inhibitor). A study by Wada et al. reported that there was a lack of correlation between anti Xa (AXA) levels and ischemic events in patients who were taking apixaban [9]. This same study concluded instead that AXA levels (high peak and/or trough) can be associated with increased risk of hemorrhagic events in patients who suffered stroke/TIA. Our patient did not have a hemorrhagic event.

Table 1. Other pertinent laboratory parameters

	Value	Normal reference range
ACE	18	8-52
Beta 2 glycoprotein I IgG Ab	<9	≤20
Beta 2 glycoprotein I IgM Ab	<9	≤20
Beta 2 glycoprotein I IgA	<9	≤20
Anti-cardiolipin IgG Ab	<9	<15
Anti-cardiolipin IgA Ab	<9	<12
Anti-cardiolipin IgM Ab	<9	<12.5
Lupus anticoagulant PTT screen	43 sec	≤40
Dilute Russel Viper Venom (Lupus)	34 sec	≤45
Beta-2 – macroglobulin	2.0 mg/L	1.0-2.6
Vit B12 level	192 pg/mL	193-986
Folate	13.8	3.1-17.5
TSH	0.434 uIU/mL	0.35-3,75

She was treated with sublingual vitamin B12 (09/25/2019 – 10/05/2019) for pernicious anemia. Patient had reported temporal arteritis which should be optimally controlled to not confound the role of this vasculitis in the recurrence of CVAs versus the atrial fibrillation alone. The decision was made in concert with Neurology and Cardiology to continue the patient on low dose aspirin (09/24/2019 – 10/05/19) in addition to switch to VKA-warfarin for thromboembolic prevention.

Deciphering with precision what may have caused this particular outcome in this case would be challenging and there are limited similar reports available. An extrapolation that could be made is based on the findings of a study by Godino et al. which showed a trend for higher number of thromboembolic events observed in patients, particularly the elderly, who were treated with inappropriate dose of NOAC [10].

Conclusion

It is unclear whether the recurrence of CVA in this case was due to inappropriate anticoagulation on apixaban or whether there are confounding factors that cannot be confidently elucidated. What is for certain is that there is limited real-world data regarding the outcomes of elderly patients treated with NOAK. More studies are needed to compare the efficacy and risk of stroke of NOAC with that of VKA in elderly patients with AF.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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