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Absent Left Anterior Descending Coronary Artery as a Potential Cause of Ischemic Stroke: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1,2 Alia Ali Alokley
EF 3 Aishah Albakr
B 4 Mohammed Almansori

1 Department of Neurology, King Fahad Hospital of the University, Al-Khobar, Saudi Arabia
2 Department of Neurology, College of Medicine, King Faisal University, Al-Ahsa, Saudi Arabia
3 Department of Neurology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
4 Department of Internal Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Corresponding Author: Alia Ali Alokley, e-mail: alia.alokley@gmail.com, aalokley@kfu.edu.sa
Conflict of interest: None declared

Patient: Male, 36-year-old
Final Diagnosis: Stroke
Symptoms: Dizziness • dysarthria • hemiplegia • seizure
Medication: —
Clinical Procedure: Coronary angiography • MRI • VSD closure surgery
Specialty: Neurology

Objective: Congenital defects/diseases

Background: Embolic stroke of undetermined source (ESUS) represents 20-30% of ischemic strokes, with a high risk of recurrence. It usually requires an extensive diagnostic evaluation to address the potential etiologies. Coronary artery anomaly (CAA) of the left anterior descending artery (LAD) is uncommon, and it is known to be linked to myocardial complications. The association of this anomaly with ischemic strokes has not been reported yet. Here, we report on a rare case of a young patient with hypoplastic LAD complicated by an impaired ventricular function that resulted in left ventricular (LV) thrombus formation as a source of recurrent ischemic strokes.

Case Report: A 36-year-old man had a 4-year history of recurrent strokes despite maintaining antiplatelet treatment. He had no pre-existing vascular risk factors or relevant family history. The initial stroke etiology work-up was inconclusive. A transesophageal echocardiogram showed moderate ventricular hypokinesia. A coronary angiogram was initiated, and a hypoplastic (LAD) artery anomaly was found. At first, the antiplatelet therapy was maintained. Later on, he presented with transient focal neurological symptoms indicative of a transient ischemic attack. Repeated echocardiograms detected left ventricular thrombus. Apixaban was started, with successful thrombus resolution in a one-month follow-up echocardiogram. He has not had a further recurrent ischemic event for 18 months.

Conclusions: This case suggests that CAAs might be considered as an associated etiology of ESUS in a young patient with recurrent cerebral events. In a clinical setting, we encourage early use of advanced cerebral and cardiac imaging modalities to accurately determine the stroke etiology, target the appropriate treatment, and prevent a further neurological sequel.

Keywords: Cerebral Arterial Diseases • Coronary Vessels • Stroke

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Background

Ischemic strokes are defined as sudden interruption of blood supply to the corresponding brain region, manifesting with symptomatic focal neurological deficit. It is categorized into multiple subtypes that aim for a better vision of a patient's prognosis, outcome, and management. These classifications are based on the Trial of Organization in Acute Stroke Treatment (TOAST), which are large-artery atherosclerosis, cardio-embolism, small-vessel occlusion, a stroke of other determined etiology, and stroke of undetermined etiology [1].

Embolic stroke of undetermined source (ESUS) represents 20-30% of all ischemic strokes. It is defined as a non-lacunar cerebral infarct with no extracranial or intracranial more than or equal to 50% stenosis in arteries supplying the ischemic area, no cardioembolic source, and no other specific causes of stroke [2]. In a clinical setting, the diagnosis of ESUS can be challenging and often requires a complete stroke work-up, including brain and vascular (head and neck) imaging modalities, echocardiogram, cardiac monitoring, and laboratory workups such as autoimmune and coagulopathy profiles [2,3]. In general, antiplatelets remain the first-line treatment option for ESUS patients. However, the optimal treatment for ESUS is still controversial; therefore, more randomized trials are required to determine the ideal management for this stroke subtype [4,5].

In a normal population, the LAD originates from the distal left main coronary artery (LMCA), which supplies the anterior part of the LV and most of the interventricular septum [6,7]. CAA of the left anterior descending artery (LAD) is an extremely rare condition that has been reported in <1% of the population [6,7]. A congenital anomaly of the origin has been found to be the most common CAAs of the LAD [8,9]. Patients with LAD anomalies are usually asymptomatic, and thus most are diagnosed incidentally. However, in some cases, anomalies of the LAD carry a risk for ventricular dysfunction, myocardial ischemia, ventricular arrhythmias, and even sometimes result in sudden cardiac death [9]. These serious CAAs need to be diagnosed to reduce the risk of morbidity and mortality. The percutaneous transcatheter arteriography (PCA) is the commonly used modality for the diagnosis of an anomalous LAD [10]. The management varies by the type of LAD anomaly present. Some require vascular intervention, while others need only medical therapy or observation [11]. This report describes a unique case of a young patient with hypoplastic LAD complicated by an impaired ventricular function that resulted in LV thrombus formation as a source of recurrent ischemic strokes.

Case Report

A 36-year-old, right-handed man had no pre-existing vascular risk factors or relevant family history for cerebrovascular disease. He denied any history of smoking, illicit drug use, or alcohol intake. His past medical history was significant for a ventricular septal defect closure at the age of 4 in addition to a 4-year history of recurrent strokes. The first ischemic event occurred in 2015. He suddenly had left-sided weakness and dysarthria. Acute ischemic stroke in the right frontal gyrus was considered based on neuroimaging. No stenosis of hemodynamic significance was found on brain and neck computed tomography angiography (CTA). Electrocardiogram (ECG) and 24-h Holter monitor demonstrated a normal sinus rhythm. Blood tests including hemoglobin, liver function, cholesterol, and homocysteine were within normal ranges. Thrombophilia screening (proteins C and S, activated protein C resistance assay, antithrombin, prothrombin, factor V Leiden and lupus anticoagulant, antinuclear, and anticardiolipin antibodies) did not show any significant abnormality. A transesophageal echocardiogram detected a typical appearance of microbubbles, with a right to left shunt indicative of patent foramen ovale (PFO), along with moderate ventricular hypokinesia. A decision was made to perform percutaneous closure of the PFO. For a long-term stroke prevention treatment plan, he was kept on aspirin 81 mg by mouth once a day. The second and third episodes of symptomatic stroke were in 2016 and 2017, respectively, presenting with sudden onset of ataxia and right hemiplegia with expressive aphasia. Three months after the last ischemic event, his wife noticed a new onset of brief episodes of blank stare, and drowsiness before regaining consciousness. He was diagnosed with post-stroke epilepsy and initiated on levetiracetam 500 mg twice daily. He was diagnosed as having post-stroke depression and was maintained on escitalopram 20 mg daily. The latest episode of the ischemic event was in August 2019, with sudden onset of dizziness, double vision, and dysarthria. This event had lasted for 1 h before he returned to his baseline status. He was referred to our hospital to identify the cause of these recurrent ischemic events.

On examination, he was vitally stable (BP 120/80 mmHg). He was conscious, alert, and oriented to time, place, and person. The neurological examination revealed expressive aphasia with spastic dysarthria and right-sided body weakness along with hemiplegic gait. He was loaded and maintained initially on dual antiplatelets (aspirin 81 mg and clopidogrel 75 mg). Brain magnetic resonance imaging sequences did not show any evidence of new infarction or hemorrhage; rather, these images further demonstrated the patient's old bilateral MCA distribution ischemic infarctions along with evidence of old lateral medullary syndrome (**Figure 1**). Computed tomography cerebral angiogram CTA did not show any stenosis or plaque formation at the intracranial vessels, except for the incidental

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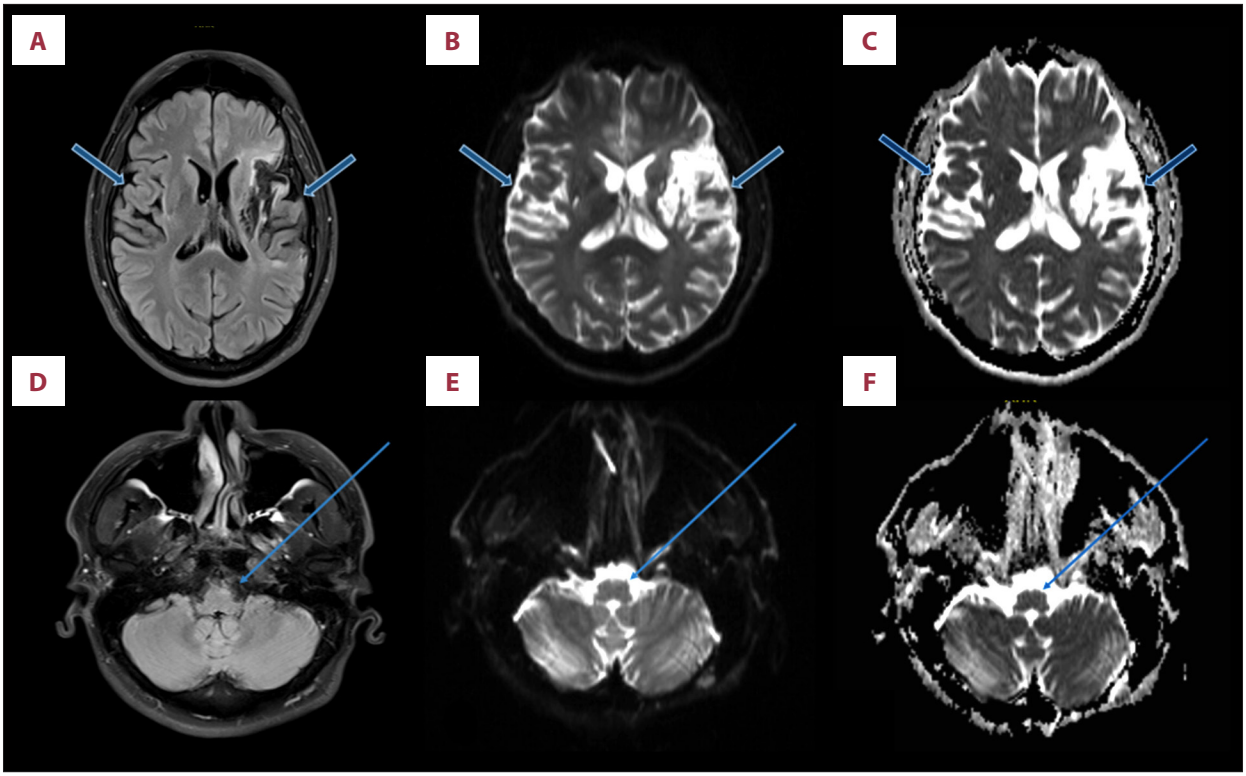

Figure 1. Brain magnetic resonance imaging (MRI); T2-weighted fluid attenuated inversion recovery (FLAIR, **A**), diffusion-weighted imaging (DWI) sequences (**B**), which showed encephalomalacia pattern with cortical and subcortical abnormal signal intensity, volume loss, and gliosis involving bilateral MCA territories, more evident on the left side, with no evidence of restriction in DWI & ADC map (**C**) keeping with old ischemic infarcts. T2-weighted fluid attenuated inversion recovery (FLAIR, **D**) showing focal area of high signal intensity in flair image at the left anterior medulla oblongata with no evidence of restriction in DWI & ADC map (**E, F**) respectively, in keeping with an old insult.

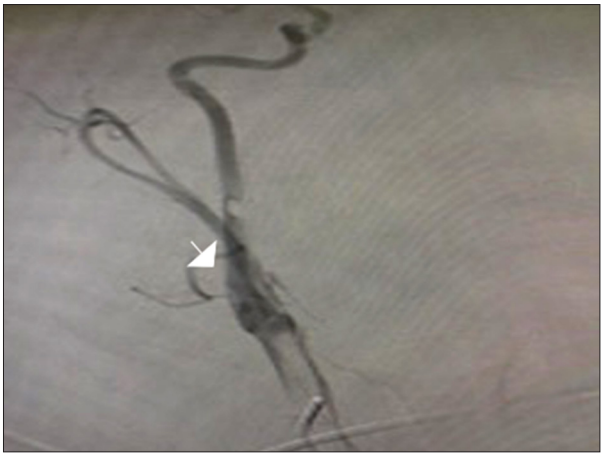

Figure 2. Cerebral angiogram Imaging showed incidental finding of the left internal carotid web with stasis of the contrast.

finding of the left internal carotid web (**Figure 2**). A neuro-interventional service was advised for stenting placement because the left internal carotid web could contribute to the patient's initial ipsilateral infarction.

Furthermore, a review of the patient's files revealed that his initial routine echocardiogram and transthoracic echocardiograms showed impaired left ventricular functions. A coronary angiogram study was then initiated, which showed an incidental finding of hypoplastic LAD. This anomaly gave rise to a compensatory large diagonal branch supplying the lateral wall at the apex. The right coronary artery was dominant, with no significant obstructive disease (**Figure 3**).

A repeated echocardiogram revealed the ejection fraction to be 50%, with global hypokinesia, and a left ventricular apical thrombus was detected (**Figure 4**). Accordingly, anticoagulation medication (therapeutic dose of low molecular weight heparin) was started, to be followed by warfarin. After a multidisciplinary team meeting with the patient and his family about the anticoagulation treatment options, we decided to start the direct factor Xa inhibitor Apixaban at 5 mg twice daily. An echocardiogram approximately 1 month after hospital discharge showed complete resolution of the left ventricular thrombus. During 18 months of follow-up, the patient was doing well, with significant improvement in his quality of life. There were no recurrent ischemic events,

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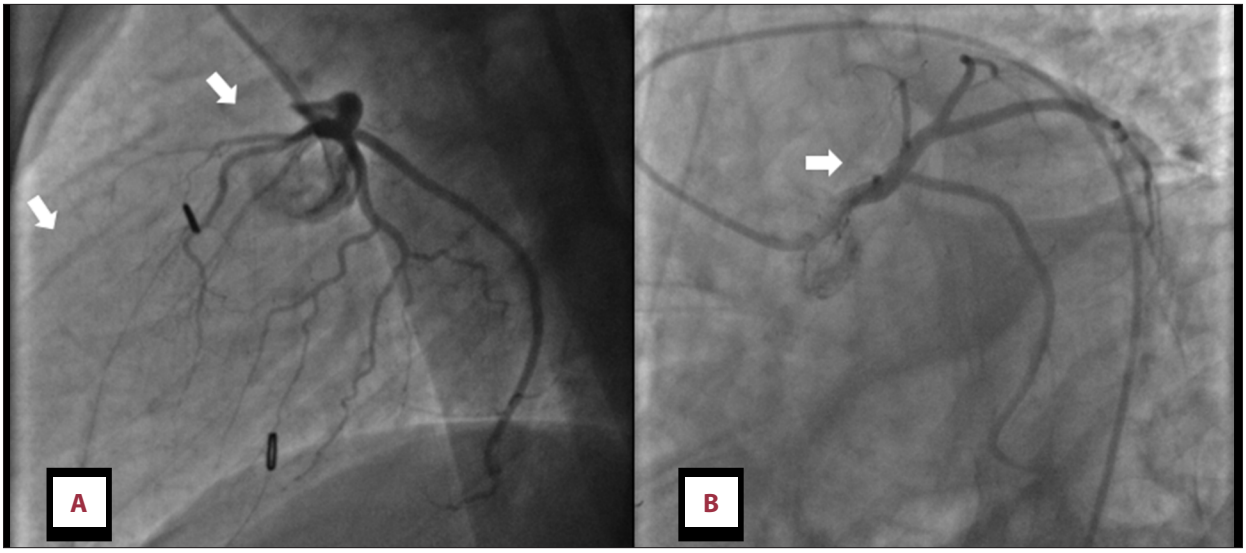

Figure 3. Coronary Angiogram Imaging: Lateral view (**A**), left anterior oblique and caudal view (**B**) of the left coronary system showing absences of the left anterior descending artery.

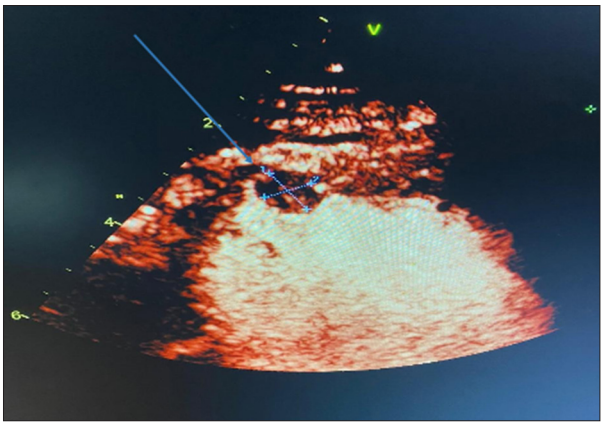

Figure 4. Echocardiogram showing left ventricular apical thrombus.

and left ventricular thrombus was not detected by echocardiogram at 18 months.

Discussion

In this paper, we report a case of recurrent ischemic events in multiple vascular territories, with negative evaluation for cardiac, small-, or large-vessel disease. His stroke subtype was qualified for ESUS, where thromboembolism is expected despite no evidence of any potential cardioembolic or atheroembolic source. Considering his high rate of recurrent strokes while on antiplatelet therapy, we thought that advanced cardiac investigation (PCI) was an essential tool in looking for other sources leading to the multiple embolic events. The presence of LV thrombus along with coronary angiography findings strongly suggested this as a possible source of ESUS.

Hypoplastic LAD, which is defined by shorter or smaller diameter than normal (<1.5 mm), has been reported in a few cases with sudden cardiac death in young people [9-12]. In the era of advanced cardiac imaging, more CAAs are being diagnosed and more variants have become important. These anomalies were frequently reported in association with other major congenital cardiac defects; for instance, our patient had a ventricular septal defect and PFO [8]. Hypoplastic LAD can be a benign condition or it can be a life-threatening condition if it affects the LAD cardiac muscle blood supply. To the best of our knowledge, this is the first reported case of CAA-related ischemic stroke, as most reported CAA-related complications were exclusive to the myocardium and heart disorders such as myocardial ischemia, heart failure, and valvular disorders [11,13]. The pathogenesis of CAA-related thromboembolism is not well understood. We hypothesized that LAD anomalies lead to impaired ventricular function or akinetic segment, thus leading to superimposed thrombosis, which may spread to the brain vasculature.

The etiology of ESUS can be the summation of multiple provoking risk factors and not necessarily be sufficient with one; also, finding one vascular anomaly in the background of multiple congenital heart defects should raise the suspicion of another alarming anomaly that may be silent for years. In our patient, an incidental finding of the internal carotid web was found on CTA. Carotid web has been linked to cases with an ipsilateral stroke of unknown etiologies [14]. We believe that the carotid web was not the main etiology for his presenting symptoms as our patient had bilateral hemispheric and brainstem strokes; thus, intervention (stenting/endarterectomy) was not a priority [15,16].

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The reported recurrence rate of ESUS is estimated to be 4-5% per year. In this case, the high recurrence rate despite antiplatelet therapy needed to be taken into consideration to prevent such sequels [3]. To date, there are no clear recommendations for the treatment of symptomatic coronary artery hypoplasia [11]. Given the nature of presumed stroke mechanism in our patient as thrombus formation, with subsequent embolization, anticoagulation therapy appears to be a logical choice in management. Use of low molecular weight heparins (LMWHs) followed by vitamin K antagonist has become the standard of care for treating LV thrombus [17], and so it was our initial plan. However, Apixaban was selected based on the patient preference given the risk of food and drug interaction with long-term warfarin use, and the substantial need for blood monitoring. Despite the limited evidence regarding the role of Apixaban in resolving LV thrombus, recent reports have indicated that Apixaban is an effective and safe treatment for patients with LV thrombus [18-21]. As shown in our patient, Apixaban has successfully resolved the LV thrombus, thus providing a potential substitute to warfarin treatment. Apixaban is a factor Xa that blocks the production of thrombin and platelet aggregation, and enhances thrombolytic properties [22]. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study showed that the use of Apixaban 5 mg twice daily was non-inferior to warfarin in reducing the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% as compared to warfarin [23]. From this point of view, we have continued our patient's care on Apixaban anticoagulation therapy for his cardiac source of recurrent ESUS. Our patient ischemic events were controlled with long-term Apixaban, and he had significant improvement with rehabilitation measures.

Conclusions

The CAA reported, in this case, is novel and provides evidence for the clinical significance of LAD hypoplasia as a cause of ESUS. This condition cannot be fully diagnosed without extensive collaboration between cardiologists and neurologists by the use of advanced imaging modalities like coronary/cerebral angiograms; however, the best long-term treatment plan is still unknown.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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