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CASE REPORT

ADVANCED

CLINICAL CASE

Transient Ischemic Attack, the Initial Presentation of Azygos to Pulmonary Vein Fistula

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ABSTRACT

There are different sources of cerebral emboli, including cardiac embolism, extracranial arterial embolism, paradoxical embolism, trauma, and iatrogenic embolism. In rare cases, atypical sources should be ruled out. We are reporting a lady who presented with transient ischemic attack and had a fistula between the azygos to the pulmonary vein. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;18:101923) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Communication between the azygos system and the pulmonary venous circulation can potentially contribute to embolic events to the brain. The risk further increases when associated with conditions that increase the pressure in the venous system leading to a right-to-left shunt. Due to hemostasis and hypercoagulable states, thrombus formation and embolism can occur, increasing the risk of transient ischemic attack (TIA) and stroke. Transient ischemic attack and stroke mediated by fistula formation between the azygos vein and the pulmonary artery is extremely rare. To our knowledge, there has only been once case reported of azygos to pulmonary vein fistula causing stroke reported in the literature.[1] Herein, we are presenting a case of anomalous communication between the azygos venous system and right pulmonary veins in a patient presenting with TIA.

LEARNING OBJECTIVES

- To be able to make a differential diagnosis of different cardiovascular situations that can cause TIA/stroke.
- To be able to differentiate between the different types of the intracardiac and the extracardiac shunts depending on the timing of the agitated saline appearance in relation with the cardiac cycles.
- To emphasize the role of different cardiac imaging modalities in the diagnosis of cardiac shunts and the vascular fistulas.

HISTORY OF PRESENTATION

A 57-year-old woman was brought to the emergency department by emergency medical services presenting with an abrupt onset of left-sided paresthesia and aphasia, which progressed to weakness over the course of several minutes. The patient's symptoms began as pins-and-needles sensation in the left upper and lower extremities. On neurological examination,

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

TEE = transesophageal echocardiogram

TIA = transient ischemic attack

the patient had decreased strength in left upper and lower extremities with 2 of 5 muscle strength in both left upper and lower extremities. Sensitivity was intact on neurological examination, and the cranial nerves did not show focal injuries. The patient denied any history of recent travel, hiking, or sick contacts. The patient denied fever, chills, and night sweats.

PAST MEDICAL HISTORY

The lady has systemic lupus, and follows up on a regular basis with a rheumatologist, hypogammaglobulinemia (on intravenous immunoglobulin therapy via Port-A-Cath), and previous deep vein thrombosis on oral anticoagulation.

DIFFERENTIAL DIAGNOSIS

The neurological findings that the patient had can be caused by thrombotic stroke or embolic TIA/stroke, especially because she has risk factors. Being on oral anticoagulation also raises the suspicion of hemorrhagic stroke. Also, it could be secondary to a lupus neurological disorder, because she has systemic lupus.

INVESTIGATIONS

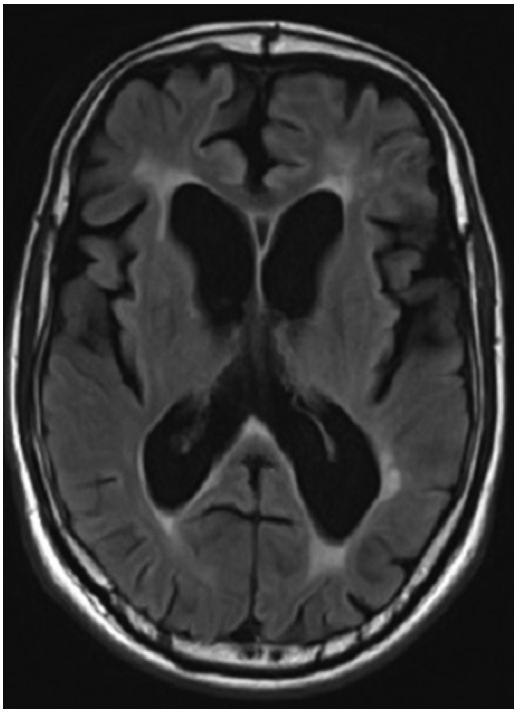
LABORATORY TESTS. Blood work-up, including complete blood count, was unremarkable, prothrombin and partial thromboplastin time were within normal limits. Total cholesterol was 226 mg/dL with low-density lipoprotein levels of 161 mg/dL; other test results were unremarkable. Antiphospholipid syndrome panel was done 3 months before the event in the outpatient setting, which was reviewed by rheumatology and found to be negative (Table 1).

TABLE 1 Antiphospholipid Syndrome Antibodies Panel

B2 glycoprotein I IgG, U/mL	<9.4	Negative <15
B2 glycoprotein I IgM, U/mL	<9.4	Negative <15
Cardiolipin IgG, GPL	2.9	Negative <15
Cardiolipin IgM, MPL	3.8	Negative <12.5
Cardiolipin IgA, APL	1.2	Negative <12
aPTT, s	46	25-37
aPTT 1:1 Mix, s	37	25-37
DRVVT screen ratio	1.46	<1.2
DRVVT confirm ratio	0.87	<1.2
DRVVT mix ration	1.27	<1.2
PT, s	23.3	9.4-12.5
INR	2.1	0.9-1.1

aPTT = activated partial thromboplastin; DRVVT = dilute Russell's viper venom time; PT = prothrombin time; INR = international normalized ratio.

FIGURE 1 Brain Magnetic Resonance Imaging



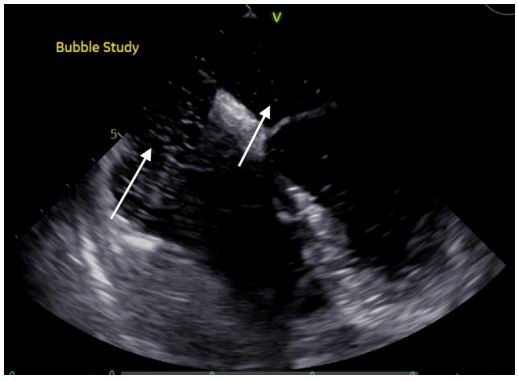
Brain magnetic resonance imaging showing T2 flair, acute infarcts in periventricular white matter.

IMAGING. Both computed tomography (CT) and angiogram of the head and the neck were unremarkable with no evidence of acute infarcts or significant stenosis or occlusion of the arteries. Magnetic resonance imaging of the brain revealed multiple small infarcts in the periventricular white matter bilaterally (Figure 1) with no evidence of acute infarcts. As part of the work-up for TIA, a transesophageal echocardiogram was done, and agitated saline bubble studies were conducted, showing simultaneous presence of bubbles in both right and left atria without evidence of intracardiac shunt (Figure 2, Video 1). These findings led to further investigation with CT angiogram of the chest showing a significant reflux of contrast into the azygos vein, occlusion of SVC distal to venous catheter, and multiple mediastinal collateral veins. One of the small collateral mediastinal veins connect the azygos vein to the right inferior pulmonary vein (Figure 3).

MANAGEMENT

Neurology started the patient on high-intensity statin and antiplatelet therapy.

FIGURE 2 Transesophageal Echocardiogram Showing Simultaneous Contrast Filling of the Left and Right Atria

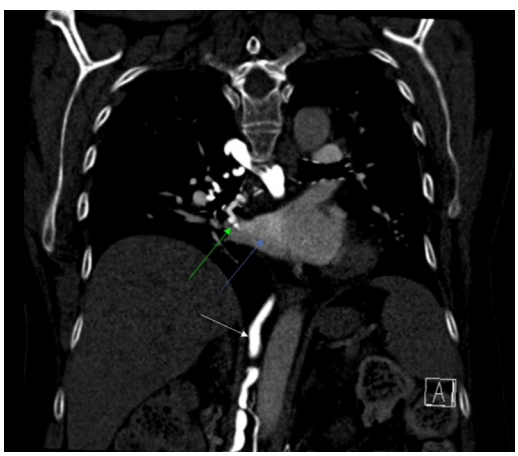


Simultaneous contrast filling of the left and right atria seen on transesophageal echocardiogram **(arrows)** with no obvious signs of atrial septal defect/patent foramen ovale or ventricular septal defect.

DISCUSSION

There are 3 common mechanisms leading to ischemic stroke: thrombosis, hypoperfusion, and embolic phenomena.[1] An embolism is a blood clot shower from the heart or arteries, or that moves paradoxically from the venous system through a shunt and settles in an cerebral artery in the brain.[2] The result is occlusion of the vessel and obstruction of oxygen and blood flow to the brain.[2] Therefore, careful evaluation and work-up for an embolic source with transthoracic or transesophageal echocardiogram is recommended in addition to Holter monitoring and vascular imaging, which are mandatory to guide appropriate evidence-based treatment and prevent recurrence of TIA and stroke.[3]

FIGURE 3 Coronal View of Computed Tomography Angiogram



Coronal view of computed tomography angiogram showing small collateral systemic vein draining into right posterior pulmonary vein **(green arrow)** with early opacification of left atrium **(blue arrow)**. There is significant reflux of contrast into the azygos and mediastinal veins.

The azygos venous system, located on either side of the vertebral column, drains the viscera within the mediastinum, back, and thoracoabdominal walls. This system consists of the azygos vein and its 2 main tributaries: the hemiazygos vein and the accessory hemiazygos vein. The azygos vein usually arises from the lumbar azygos vein or the posterior side of inferior vena cava around the level of renal veins. It passes through the diaphragm and mediastinum, and drains into the superior vena cava.[4] The azygos venous system has many anastomoses along the inferior vena cava and vertebral venous plexuses. These connections allow alternate drainage routes between the 2 venae cavae in case of inferior vena cava or superior vena cava obstruction.[5]

Conditions such as heart failure, portal hypertension, right atrial thrombus, pulmonary embolism, arteriovenous fistula, and in our case, superior/inferior vena cava obstruction can lead to enlargement of the azygos vein.[6] Obstruction of the superior vena cava can occur in up to 40% of patients with central catheters. Only 1% to 14% of these patients develop SVC syndrome with an estimated rate of 0.003% to 0.2% for each day the catheter resides in the SVC.[7] CT angiogram remains the cornerstone in diagnosing azygos vein enlargement and recognizing the etiology of the disease.[6] In this case, CT angiogram of the chest revealed SVC obstruction secondary to a malfunctioned Port-A-Cath, with significant enlargement of the azygos vein and patent fistula between a branch of the azygos vein branches and the right lower pulmonary vein.

Transesophageal echocardiogram (TEE) with agitated saline is considered the gold standard for the evaluation of embolic stroke of undetermined source; however, routine application of TEE is often limited in patients with acute stroke because of acute illness, mental status change, coagulopathy or bleeding tendency, and lack of patient cooperation.[8] The usage of the agitated saline helps determine if the shunt is intracardiac or intrapulmonary depending on the number of the cardiac cycles. The bubbles will appear on the left side after 3 to 5 beats in the former shunt and after 5 beats in the latter.[9] In our case, TEE with agitated saline showed simultaneous appearance of

the bubbles in the right and left sides of the heart without evidence of an intracardiac shunt, suggesting the presence of direct connection between the systemic and pulmonary venous systems.

Normally, the pressure in the pulmonary venous system is higher than the pressure in the vena cava. However, chronic obstruction of the SVC can lead to a significant increase in pressure in the systemic venous system leading to reversal of the shunt. In this case, the increased pressure reverses the flow from the azygos vein to the pulmonary vein through the fistula. This reversal is further increased with Valsalva.

Stroke can be also one of the manifestations of systemic lupus. Usually, they occur early in the disease, and patients should have involvement of other organs.[10] Previous studies correlate the incidence of these neurological ischemic events with the persistent high titers of different lupus and antiphospholipid antibodies.[11] The absence of positive antibodies or the involvement of other organs makes the autoimmune disease less likely to be the cause of the patient's symptoms.

In this case, we present a patient presenting with cerebral embolic infarction secondary to a very rare cause. The chronic obstruction in the superior vena cava that occurred secondary to a nonfunctional Port-A-Cath is theorized to be the cause of the embolic event. The chronic obstruction is theorized to have caused an aneurysmal enlargement of the azygos vein and angiogenesis with fistula formation between the azygos vein and right lower pulmonary vein. Through literary review, this case is very rare with only 1 similar case reported to date.

Due to the rarity of these cases, there are no clear guidelines for management and treatment. The literature suggested treating the azygos to pulmonary vein fistula as a pulmonary arteriovenous fistula.[12] Pulmonary arteriovenous malformations <2 cm in diameter with afferent arteries >3 mm in diameter have been documented to cause TIAs, strokes, and brain abscesses throughout the literature. Treatment is recommended for all pulmonary arteriovenous malformations with single feeding vessels 3 mm to reduce the risk of paradoxical embolization.[13] In addition, anticoagulation is recommended to prevent further episodes.[13]

FOLLOW-UP

After being discharged, the patient presented for follow-up. She denied any new neurological symptoms, and had a normal physical examination. The Port-A-Cath was changed successfully, and the patient is compliant with her medications including the antiplatelet therapy.

CONCLUSIONS

There are several etiologies leading to TIA and strokes including embolic events. The most common sources are cardiac thrombus, arterial thrombus, and iatrogenic and paradoxical shunts from the venous system. The most common shunts reported in literature are intracardiac, like patent foramen ovales, ventricular septal defects, and atrial septal defects, or intrapulmonary secondary to arteriovenous malformations. It is extremely rare to have fistulization between the azygos vein and the pulmonary vein. Herein, we are reporting a very unique case of a patient presenting with TIA, found to have an azygos vein to right pulmonary vein fistula in the presence of superior vena cava obstruction. To date, only one case has been reported previously.

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REFERENCES

1. Ibrahim F, Murr N. *Embolic Stroke*. StatPearls; October 2022.

2. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev*. 2010;6(3):150–161.

3. Roth EJ. Cerebral embolism. *Encycl Clin Neuropsychol*. 2011:530–531.

4. Donohue JR, Daly DT. *Anatomy, Thorax, Azygos Veins*. StatPearls, July 2022.

5. Piciucchi S, Barone D, Sanna S, et al. The azygos vein pathway: an overview from anatomical variations to pathological changes. *Insights Imaging*. 2014;5(5):619–628.

6. Shin MS, Ho KJ. Clinical significance of azygos vein enlargement: radiographic recognition and etiologic analysis. *Clin Imaging*. 1999;23(4):236–241.

7. Rice TW, Rodriguez RM, Light RW. The superior vena cava syndrome: clinical characteristics and evolving etiology. *Medicine (Baltimore)*. 2006;85(1):37–42.

8. Droste DW, Schmidt-Rimpler C, Wichter T, et al. Right-to-left-shunts detected by transesophageal echocardiography and transcranial Doppler sonography. *Cerebrovasc Dis*. 2004;17(2-3):191–196. https://doi.org/10.1159/000075790

9. Porter TR, Abdelmoneim S, Belcik JT, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a

focused update from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2014;27(8):797–810. https://doi.org/10.1016/j.echo.2014.05.011

10. Nikolopoulos D, Fanouriakis A, Boumpas DT. Cerebrovascular events in systemic lupus erythematosus: diagnosis and management. *Mediterr J Rheumatol*. 2019;30(1):7.

11. Chaves CJ. Stroke in patients with systemic lupus erythematosus and antiphospholipid antibody syndrome. *Curr Treat Options Cardiovasc Med*. 2004;6(3):223–229.

12. Huang Y, Sun W, Li F, Sun W. Azygos vein to pulmonary vein fistula is a pathway for cerebral embolism. *Chest*. 2010;138(3):726–729.

13. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet*. 2011;48(2):73–87.

KEY WORDS azygous-to-pulmonary vein fistula, cardiovascular imaging, echocardiography, stroke

APPENDIX For a supplemental video, please see the online version of this paper.