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A young man with acute weakness of his right arm

A 42-YEAR-OLD MAN was working at his computer when he suddenly became disoriented and lightheaded, had difficulty concentrating, and could not move his right arm. He could walk without difficulty, but he had a tingling sensation in his right leg. He did not lose consciousness or have any associated palpitations, chest pain, shortness of breath, nausea, vomiting, headaches, or visual changes.

He called 911, and an ambulance arrived 15 minutes later. By that time his symptoms had started to resolve. Now, in the emergency department, his only residual symptom is mild numbness of his right arm and shoulder.

Until now he has been healthy except for a history of dyslipidemia. He takes no prescription or over-the-counter medications and has no drug allergies. He has smoked one pack of cigarettes daily for the past 28 years and also smokes marijuana several times each month. He drinks alcohol occasionally. His family has no history of stroke, premature coronary artery disease, or sudden cardiac death.

■ INITIAL EVALUATION

His heart rate is 88 beats per minute, blood pressure 142/82 mm Hg, and blood oxygen saturation 98% while breathing room air. He is alert and in no acute distress and answers questions appropriately.

His breathing sounds are normal, without crackles or wheezes. His heart has normal first and second sounds, a normal rate and rhythm, and no extra sounds or murmurs. His abdomen is normal. His extremities are warm and well perfused with normal peripheral pulses and no edema.

On neurologic examination, his cranial

nerves and visual fields are normal, and his strength is normal in all muscle groups except for the right upper arm, which is slightly weaker than the left when tested against resistance. Reflexes and response to light touch and pinprick are normal.

His serum chemistry levels, renal function, and blood counts are normal. His total cholesterol level is 155 mg/dL, high-density lipoprotein cholesterol 38 mg/dL, low-density lipoprotein cholesterol 108 mg/dL, and triglycerides 1,286 mg/dL. Electrocardiography is normal with sinus rhythm at a rate of 74.

Magnetic resonance imaging (MRI) of the head and neck with magnetic resonance angiography (MRA) of the intracranial and extracranial vessels is performed. Diffusion-weighted images show a hyperintense lesion in the left insular cortex, consistent with an infarct in the distribution of a branch of the left middle cerebral artery. There is no intracranial hemorrhage. All intracranial and extracranial major vessels are patent, and no stenoses are seen.

■ DIFFERENTIAL DIAGNOSIS

1 Which is the most likely cause of this patient's stroke?

- ☐ Vertebral or carotid atherosclerosis
- ☐ Cervical arterial dissection
- ☐ A hematologic disorder
- ☐ Cocaine abuse
- ☐ Cardiac embolism

Atherosclerosis

Although 85% of all strokes are ischemic, and most ischemic strokes are caused by occlusive atherosclerosis of large vessels, most ischemic

A previously healthy, relatively young man has had a stroke. What is the cause, and what should be done?

strokes occur in patients older than 65 years. In patients younger than 55 years, only about 10% of strokes are caused by large-vessel atherosclerotic disease, thus lowering the initial probability that this is the cause of our patient's stroke.¹ Furthermore, our patient's MRA study showed no carotid artery stenoses, which effectively eliminates this as the cause of his stroke, as the diagnostic sensitivity of MRA for detecting carotid stenosis is approximately 97%.

Cervical arterial dissection

Cervical arterial dissection causes up to 20% of strokes in patients younger than 45 years.² Dissections usually involve the extracranial portion of the vessel, and involve the internal carotid arteries at least three times as often as the vertebral arteries. In many cases the dissection is preceded by mild neck trauma, which may be as minor as a vigorous cough or turning of the head.

Typical features of dissection include neck pain, headache, and Horner syndrome, followed minutes to hours later by symptoms of ocular or cerebral ischemia, usually a transient ischemic attack rather than a stroke. Neurologic symptoms are most commonly due to thrombosis at the dissection site with distal embolization. Inherited disorders that are associated with increased risk of cervical arterial dissection include Ehlers-Danlos syndrome type IV, Marfan syndrome, autosomal-dominant polycystic kidney disease, osteogenesis imperfecta type I, and fibromuscular dysplasia.³ MRA and computed tomographic angiography are the diagnostic tests of choice.

Our patient's symptoms began suddenly, without a history of trauma or neck pain, making arterial dissection less likely as the cause of his stroke. No dissection was seen on MRA, which also minimizes its likelihood.⁴

Hematologic disorders

Many hematologic disorders are associated with ischemic stroke. The disorders most likely to cause ischemic stroke in patients younger than 45 years are antiphospholipid antibody syndrome, sickle cell anemia, and heparin-induced thrombocytopenia,⁵ which are associated with arterial thrombosis.

Most of the common hereditary hyperco-

agulable disorders, such as factor V Leiden/activated protein C resistance, the prothrombin gene mutation (G20210A), antithrombin III deficiency, protein C deficiency, and protein S deficiency, typically cause venous thrombosis much more often than they cause arterial thrombosis. Thus, the most typical presentations of stroke in these disorders are cerebral venous thrombosis or paradoxical embolic stroke due to a patent foramen ovale. Antithrombin III deficiency and protein C and protein S deficiency have been associated with arterial thrombosis, but so infrequently that their likelihood in this patient is extremely low.

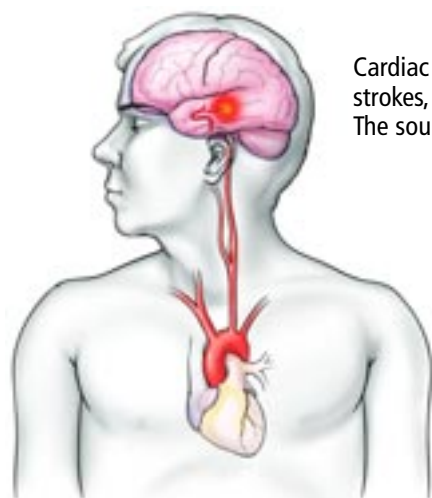
Clues to the diagnosis of a hypercoagulable state include venous thrombosis in the past, recurrent fetal loss, thrombocytopenia, livedo reticularis, antiphospholipid antibody syndrome, and skin necrosis at the start of oral anticoagulant therapy.

Of importance: the relationship between hereditary hypercoagulable disorders and stroke is considerably weaker than their association with venous thrombosis. Several studies in clinical and general populations have failed to show an independent association between stroke and protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden/activated protein C resistance, or the prothrombin G20210A mutation.⁶⁻⁸ Therefore, most experts do not recommend screening all stroke patients for a hypercoagulable state—only those with a personal or family history of thrombosis or young patients with unexplained stroke.

Our patient does not have historical or clinical features that would suggest a specific hypercoagulable disorder, either acquired (eg, heparin-induced thrombocytopenia) or inherited. A laboratory workup for a hypercoagulable disorder would likely be of little value in determining the cause of his stroke, and even if a hereditary disorder were identified it would be difficult to determine causation. However, if no other explanation for his stroke can be found during the workup, one could consider testing for proteins C and S, antithrombin III, activated protein C resistance (and factor V Leiden if screening for activated protein C resistance is positive), prothrombin G20210A, fibrinogen, homocysteine, D-dimers, and antiphospholipid antibodies.

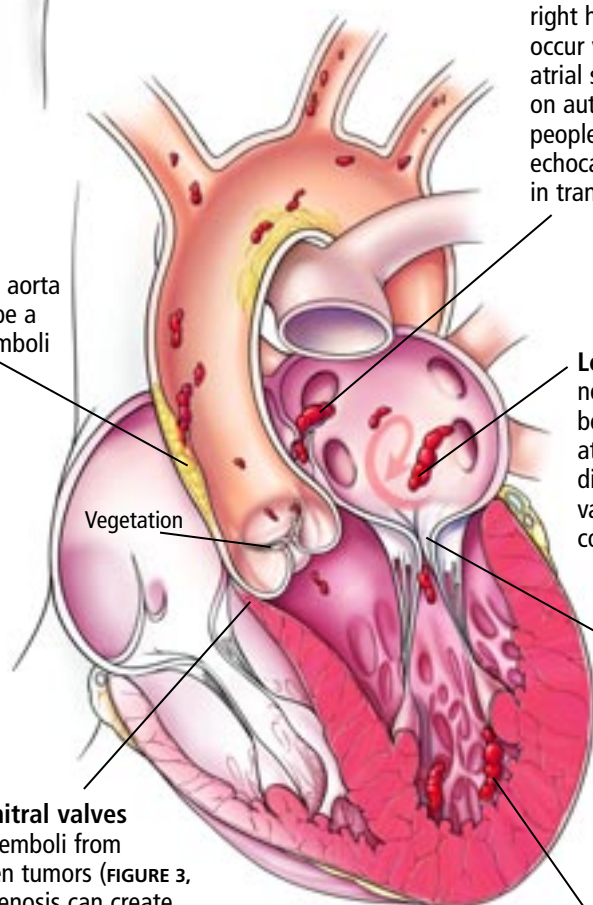
Most inherited hypercoagulable disorders cause venous, not arterial thrombosis

■ Cardiac sources of embolism



Cardiac sources of embolism account for up to 20% of all strokes, and an even higher percentage in younger patients. The sources vary.

Atherosclerosis of the aorta or carotid arteries can be a source of both atheroemboli and thromboemboli.



Paradoxical embolization from the right heart to the left is believed to occur via a patent foramen ovale or atrial septal defect (which can be found on autopsy in up to one fourth of all people). In **FIGURE 2**, transesophageal echocardiography reveals an embolus in transit.

Left atrial thrombi account for nearly half of cardiac thromboemboli. The most common cause is atrial fibrillation; other causes are dilated cardiomyopathy, mitral valve stenosis, and some hypercoagulable states.

Stenotic mitral valve

The aortic and mitral valves can be sources of emboli from vegetations or even tumors (**FIGURE 3**, **FIGURE 4**); mitral stenosis can create stasis and lead to thrombus formation.

Left ventricular thrombi are a common complication of myocardial infarction, due to areas of hypokinetic myocardium.

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FIGURE 1

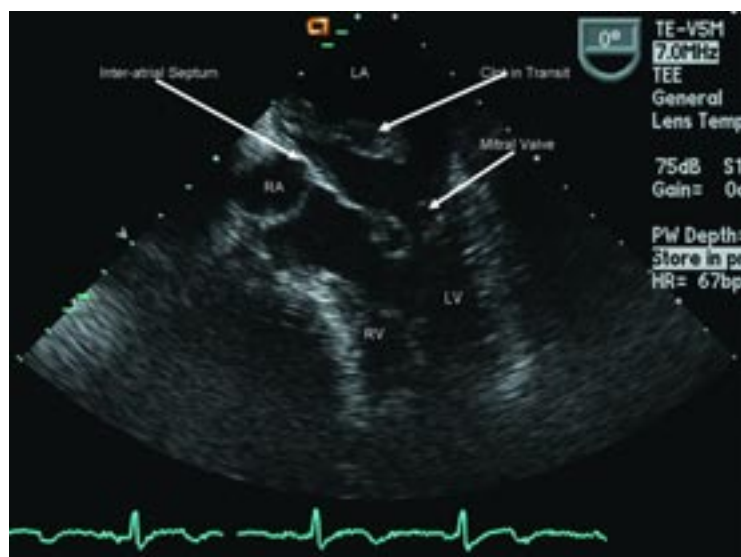


FIGURE 2. Transesophageal echocardiogram in a patient who presented with presyncope (and who had a high-probability ventilation-perfusion scan) shows a clot in transit between the right atrium and left atrium. RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle.

Up to 20% of strokes are of cardiac embolic origin, and even more in young patients

Cocaine abuse

Another important cause of ischemic stroke is the use of sympathomimetic drugs such as cocaine or amphetamines. The strongest association is with cocaine, which has been seen in case series to cause cerebral vasoconstriction in a dose-dependent manner. Vasoconstriction is also related to a longer duration of cocaine use.⁹ Several case-control studies have found that the risk of stroke is 4.5 to 6.5 times higher in drug abusers than in controls, and that use of catecholamines or cocaine alone was associated with a significantly increased risk of stroke.^{10,11}

It is certainly advisable to ask about the use of illicit drugs and to send serum and urine samples for appropriate drug screening in young stroke patients, particularly if another cause cannot be found or if drug use is suspected.¹²

Cardiac embolism

Cardiac embolism is the most likely cause of the stroke in this patient. Up to 20% of the 500,000 strokes that occur annually in the United States are of cardiac embolic origin,¹³ and the prevalence is even higher in younger

patients. In a registry of 428 strokes in patients 15 to 44 years of age, a cardiac source of embolism was the cause in 31.8%.¹⁴

Cardiac causes of embolization (**FIGURE 1**) can be categorized as:

- Masses, which include atherosclerotic plaques, cardiac tumors, and infective and noninfective valvular vegetations
- Passageways for paradoxical embolism, such as a patent foramen ovale or atrial septal defect (**FIGURE 2**)
- Stasis in the left atrium or left ventricle, with a resulting propensity for thrombosis.

Of these, the most common are left atrial and left ventricular thrombi and aortic atherosclerosis.¹⁵

Atrial thrombus is most often seen in patients with atrial fibrillation, mitral stenosis, or dilated cardiomyopathy. Echocardiography of the left atrium in patients with these conditions often reveals spontaneous echo contrast that resembles swirling “smoke,” which is thought to be produced by red blood cell aggregation due to blood stasis. This sign is strongly associated with left atrial thrombi.

Left ventricular thrombosis is one of the most common complications of myocardial infarction and is caused by blood stasis in regions of the ventricle in which the myocardium is hypokinetic or akinetic.

We cannot assume, however, that a potential cardioembolic source seen on echocardiography is the cause of a given patient’s stroke. The evidence proving a causal relationship between most potential cardiac embolic sources and stroke is less than robust. Most of the published data are from nonrandomized studies or case series, and there are no large, prospective studies available to clearly prove that a given cardioembolic source is directly related to embolic stroke.¹⁶

This being said, most studies have found high prevalence rates of cardioembolic sources in patients with embolic stroke, which suggests that a causative relationship may exist. However, many of these findings also have a relatively high prevalence among the general population without stroke, raising the possibility that the finding could be incidental and unrelated. Examples are

patent foramen ovale, which exists in 27% of adults,¹⁷ and aortic arch atheroma, which is common in the elderly.

In the end, when the only potential source of embolism that can be found is in the heart (as is often the case in younger patients), the probability is much greater that it is indeed the cause of the stroke. The lack of direct evidence linking many sources of cardioembolism to stroke emphasizes the need for a thorough investigation of all possible causes of stroke.

■ DIAGNOSTIC EVALUATION

2 Which is the best study to evaluate for a cardiac embolic source in this patient?

- ☐ Transthoracic echocardiography (TTE)
- ☐ Transesophageal echocardiography (TEE)
- ☐ Transcranial Doppler ultrasonography
- ☐ Electrocardiography

The study of choice in this patient is TEE. Overall, TEE is better than TTE in identifying a cardiac source of embolism,^{18,19} mainly because the images are obtained from a probe in the esophagus, which is in close proximity to the heart, so that there is little additional soft tissue and bone between the probe and cardiac structures. In addition, higher-frequency probes can be used. Both of these result in ultrasonographic images with much greater spatial resolution than can be obtained with a transthoracic study.¹⁵

In a case series,²⁰ TEE identified a potential cardiac source of embolism in 45 (57%) of 79 patients with cryptogenic stroke, compared with only 12 (15%) with TTE.

The main limitation of TEE is that it does not show the left ventricular apex very well, making an accurate assessment of left ventricular function or identification of a left ventricular apical thrombus much less likely.

In patients who lack evidence of atherosclerotic cerebrovascular disease, specific findings on history or physical examination could increase the chances of identifying an embolic source, such as left ventricular thrombus, on TTE. These findings could include a history of a myocardial infarction, congestive heart failure, left ventricular dysfunction, endocarditis, rheumatic heart dis-

ease, a prosthetic valve, or atrial fibrillation or flutter. TTE by itself is considered sufficient for making the diagnosis of mitral stenosis, left ventricular aneurysm, dilated cardiomyopathy, left ventricular thrombus, and mitral valve prolapse with myxomatous degeneration of the leaflets.

However, in patients without signs or symptoms of cardiac disease, the diagnostic value of TTE is significantly less. Several studies have demonstrated that in patients without evidence of cardiac disease, TTE identifies the source of embolism less than 10% of the time.²¹ Some series even suggest that the yield may be less than 1%.²² TEE has the advantage of being able to diagnose the above disorders and of having a higher sensitivity for identifying potential sources that may be missed by TTE, such as left atrial or left atrial appendage thrombus, aortic arch atheroma, patent foramen ovale, atrial septal aneurysm, or spontaneous echo contrast. It should be remembered, however, that TEE is a semi-invasive procedure that carries the risks of both the procedure and the sedation, eg, bronchospasm, hypoxia, arrhythmias, upper gastrointestinal trauma, and bleeding.²³

Further clouding the decision are recent advances in TTE technology, such as contrast TTE with second harmonic imaging, which enhances the ability of TTE to identify potential sources of stroke such as patent foramen ovale nearly to the level of TEE.²⁴

Unfortunately, guidelines from professional societies do not offer assistance on the best diagnostic approach. Current guidelines from the American Heart Association, American College of Cardiology, and American Society of Echocardiography do give echocardiography a class I indication in younger patients (< 45 years old) with cerebrovascular events or older patients (> 45 years old) with stroke without evidence of cerebrovascular disease or other obvious causes. However, there is no official recommendation on whether to choose TTE, TEE, or both studies.¹⁶ Given the multiple causes of cardioembolism and the variety of clinical factors that could influence the decision to choose a certain echo study, this decision is appropriately left to the individual physician.

We cannot assume that a potential cardioembolic source is the cause of a given patient's stroke



FIGURE 3. Left, transesophageal echocardiogram of aortic valve in short-axis view shows papillary fibroelastoma (arrowhead) attached to right coronary cusp. Right, long-axis view.

A reasonable, evidence-based diagnostic approach in young stroke patients is to proceed to TEE when routine TTE and electrocardiography are unrevealing.²⁵ In reality, this is the practice followed in most centers, including ours. Although TTE has a lower diagnostic yield in patients without symptoms, it has the advantages of being readily available in most centers, being noninvasive, and providing complementary information to TEE even when TTE does not reveal a potential cause of stroke.

As for the other studies:

Electrocardiography is valuable in identifying potential cardioembolic causes of stroke such as atrial fibrillation, left ventricular aneurysm, or myocardial infarction, but it is insufficient by itself to assess for many other potential sources of cardioembolism.

Transcranial Doppler ultrasonography is very sensitive for detecting patent foramen ovale and other right-to-left shunts that could be sources of cardioembolism. In this test, microbubbles from agitated saline are injected into the venous circulation and are detected in the cerebral arteries after passing through the shunt. It has no utility in identifying the other possibilities discussed above, nor can it discriminate whether these shunts are intracardiac or extracardiac.

Case continued

The patient undergoes TTE, which shows normal left ventricular size, wall thickness, and systolic function. His right ventricular function is normal, as are his left and right

atrial size. Valvular function is normal, and no right-to-left interatrial shunt is detected with the use of agitated saline contrast.

The patient then undergoes TEE, which reveals a 9- by 8-mm mobile soft-tissue mass attached to the aortic side of the aortic valve at the junction of the right and left coronary cusps (**FIGURE 3**). There is trivial aortic insufficiency, and the rest of the aorta appears normal. This lesion is consistent with a valvular papillary fibroelastoma.

MANAGEMENT

3 Which is the most appropriate way to manage the lesion?

- ☐ Surgical resection
- ☐ Periodic echocardiographic follow-up
- ☐ Anticoagulation and periodic echocardiographic follow-up

Cardiac papillary fibroelastomas are rare benign primary tumors of the heart. The true incidence is unknown because, when small, they can be asymptomatic and easily overlooked on gross examination. In adults, they are the second most common primary cardiac tumors, next to atrial myxoma.²⁶

These tumors primarily affect the valves (most often the aortic valve), and consist of a small, highly papillary, avascular tumor covered by a single layer of endothelium, containing variable amounts of fine elastic fibers arranged around a central hyaline stroma (**FIGURE 4**).²⁷ Most of the tumors are sessile, while a few are attached to the valve by a short stalk.

No official guidelines exist on the choice of TTE vs TEE for assessing potential causes of stroke

The histogenesis is not known, but the mean age at which they are detected is approximately 60 years, and most of the patients are men, likely because most of these tumors are found incidentally during echocardiography, open heart surgery, or autopsy.²⁸

Most patients with cardiac papillary fibroelastomas have no symptoms; however, those who do have symptoms usually experience valve obstruction or embolization of tumor fragments, leading to stroke, myocardial infarction, or sudden death. Further increasing the risk of embolism, thrombus has been reported on the surface of some tumors, supporting the use of anticoagulation in patients who have experienced embolic phenomena.²⁹

A case review of 725 patients with these tumors²⁷ found that tumor mobility and location on the aortic valve were univariate predictors of tumor-related death and of nonfatal embolism. The only independent predictor of tumor-related death or nonfatal embolization was tumor mobility.

Surgical resection of the tumor is curative, and no recurrences have been reported, although the longest follow-up period has been 11 years.

Although no data exist to support the practice, patients with nonmobile or nonaortic valve tumors could be managed with anticoagulation and periodic echocardiographic follow-up until the tumor becomes mobile or symptomatic, but such a conservative strategy would seem inappropriate for our patient. His tumor is both mobile and located on the aortic valve, putting him at risk of death, and he has already experienced an embolic complication. Therefore, his lesion should be surgically resected.

Case continued

The patient receives anticoagulation therapy with subcutaneous enoxaparin (Lovenox) and warfarin (Coumadin). He undergoes successful surgical resection of the tumor without complication and is discharged to home on hospital day 5.

TAKE-HOME POINTS

The potential causes of stroke in patients younger than age 45 differ significantly

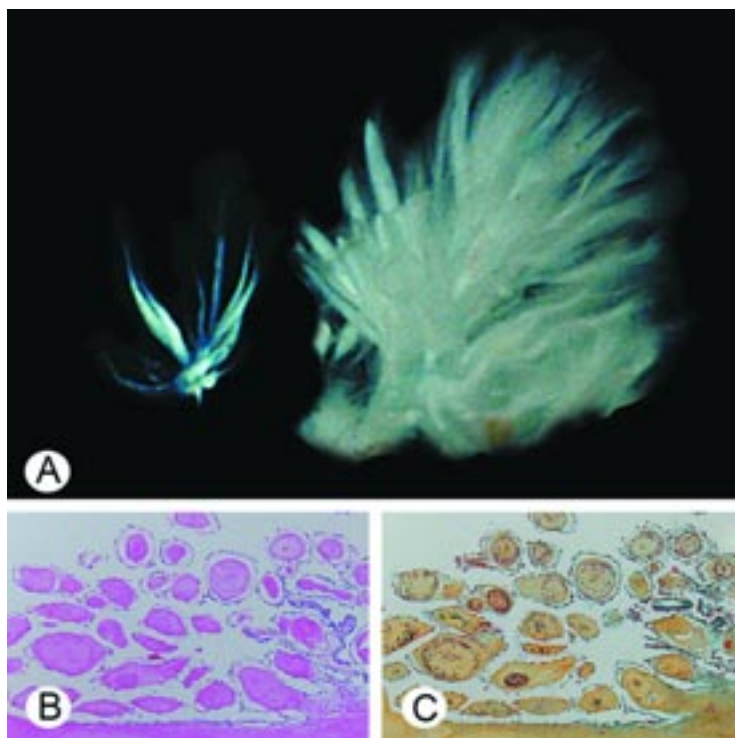


FIGURE 4. A, papillary fibroelastomas are composed of fine and coarse branching fingerlike projections that usually arise on valve surfaces. B, the papillary fronds are avascular and composed of dense collagenous cores covered by a single layer of endothelium (hematoxylin and eosin). C, a Movat pentachrome stain shows elastic fibers within the fibrous core (elastin—black; collagen—yellow).

from those in older patients. Cardiac embolism is the most frequent cause of stroke in young patients and is most often from left atrial or ventricular thrombus or from aortic atheroma.

In young patients, TEE is superior to TTE in identifying a specific source of cardiac embolism, particularly when clues from the history or physical examination are lacking and the preliminary diagnostic workup fails to identify the cause of the stroke.

Our patient's history, physical examination, MRI, MRA, electrocardiography, and TTE all failed to disclose a probable cause of his stroke. Appropriately, TEE was performed, which confirmed the diagnosis of cardiac papillary fibroelastoma, a rare and benign primary tumor of the heart with the potential for disastrous consequences. ■

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