Embolic Stroke Secondary to an Indwelling Catheter in a Patient With a Patent Foramen Ovale: A Case Report and Review of the Literature

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Case Report

A 58-year-old white woman with non–small cell lung cancer, stage IIIB (T4 N2 Mx) presented with a 1-day history of dysnomia, difficulty in finding words, and confusion. The patient had been diagnosed with lung cancer 4 months earlier, when a lung mass was identified incidentally during a routine chest x-ray. Further investigation by computed tomography (CT) showed a 3.2-cm mass and a 1-cm satellite lesion in the right upper lobe, as well as enlarged mediastinal lymphadenopathy. Biopsy revealed adenocarcinoma consistent with a lung primary tumor. A positron emission tomography (PET) scan demonstrated no evidence of metastatic disease, and magnetic resonance imaging (MRI) of the brain was also negative for metastatic disease. The patient was therefore staged as T4 N2 Mx (stage IIIB). Her medical history was otherwise unremarkable. Specifically, she had no history of diabetes, hypertension, hyperlipidemia, or cardiovascular disease. She subsequently had a Medi-Port catheter placed in preparation for chemotherapy, and then received weekly carboplatin (Paraplatin, Bristol-Myers Squibb) and paclitaxel (Taxol, Bristol-Myers Squibb) and concurrent chest radiation for 7 weeks, followed by 2 cycles of an every-3-week regimen of carboplatin and paclitaxel. She tolerated the treatment without any serious complications, and her European Cooperative Oncology Group (ECOG) performance status remained zero throughout.

The day following her second cycle of every-3-week carboplatin and paclitaxel, she developed the sudden onset of confusion, dysnomia, and agraphia. She denied any headaches, sensory abnormalities, decrease in motor strength, numbness, dizziness, weakness, imbalance, seizures, tremors, or loss of consciousness. Her physical examination was notable only for confusion with complicated commands, dysnomia, trouble with word finding, and right and left confusion. Neurologic examination was otherwise nonfocal. MRI of the brain revealed patchy cortical/subcortical fluid attenuated inversion recovery (FLAIR) hyperintensities, with restricted diffusion and gyriform cortical enhancement within the left temporoparietal lobe, suspicious for a subacute distal left middle cerebral artery distribution infarct. There was no evidence of brain metastases.

The patient was subsequently placed on aspirin and admitted to the hospital for further evaluation. Extensive work-up for a thromboembolic source was unrevealing; tests included magnetic resonance angiography of the head/neck, transthoracic echocardiogram, hypercoagulability work-up, CT chest angiography, and Doppler ultrasound of the lower extremities.

Due to continued concern regarding an embolic source, a transesophageal echocardiogram with bubble study was performed. The results showed several small, mobile echodensities (Figure 1, arrow) attached to the patient's Medi-Port catheter (Figure 1, arrowhead), in addition to a patent foramen ovale (PFO) with a small left-to-right shunt shown at rest with color Doppler imaging. The bubble study confirmed the shunt, which was present while the patient was at rest, coughing, and performing a Valsalva maneuver (Figure 2). Additional findings included a mild atherosclerotic plaque in the ascending and descending thoracic aorta. The patient began anticoagulation with warfarin to treat the central venous catheter thrombosis. Over the next several weeks, her neurologic symptoms improved substantially. Follow-up transesophageal echocardiography was performed 2 months later, which showed no further evidence of central venous catheter thrombosis. At that time, the catheter was removed without incident and anticoagulation was discontinued.

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Discussion

Individuals with cryptogenic strokes and PFO account for up to 100,000 cases of ischemic stroke per year. The high incidence of PFO has led to questions about its significance and association with stroke. Furthermore, even with the finding of a PFO, a source of the thrombus must be identified to determine if the PFO is a contributing factor to the stroke.

Clinical Features and Diagnosis of PFOs

The PFO, a vestige of the fetal circulation, is an interatrial opening arising from the failure of the septum primum and secundum to fuse after birth.[1] It serves as a 1-way flap that allows right-to-left blood flow when right atrial pressure exceeds that of the left, providing direct passage into arterial circulation. In individuals without PFOs, matter in the venous circulation is filtered via the capillaries in the lung and does not gain access into the arterial circulation. However, with a PFO, the filtering function of the lung is bypassed. This may allow entry of a paradoxical embolism, which refers to the passage of a thrombus or other embolic particles from the venous circulation directly into the arterial circulation through a right-to-left shunt.[2,3]

If there is concern for a possible PFO, 3 methods are commonly used for its diagnosis: transthoracic echocardiography, transesophageal echocardiography, and transcranial Doppler. Of these imaging modalities, transesophageal echocardiography is superior, with a sensitivity of 89% and specificity of 100%, as compared to a sensitivity of 50–60% with a transthoracic echocardiography.[3] Furthermore, transesophageal echocardiography provides the ability to directly visualize the PFO and additional atrial and aortic sources of emboli, such as aortic arch atherosclerosis or, in this case, upper limb deep venous thrombosis. With these advantages, the transesophageal echocardiography has become the study of choice for PFO detection.

With the development of transesophageal echocardiography, the prevalence of PFOs was found to be higher than previously recognized, occurring in up to 27% of nonselected individuals.[1,4] Its presence in cryptogenic stroke is consistently overrepresented as well, being seen in up to 50% of stroke patients, which raises the question of whether a paradoxical embolus is the cause of stroke in these patients.[3,4] Case control studies showed a higher frequency of PFOs in cryptogenic stroke patients versus the control population. This finding was later confirmed by multiple meta-analyses, one of which showed an odds ratio of 5.01 when comparing the likelihood of a PFO occurring in a patient with cryptogenic stroke versus a stroke-free individual.[5] However, even with this apparent association with stroke, the thrombus must be identified.

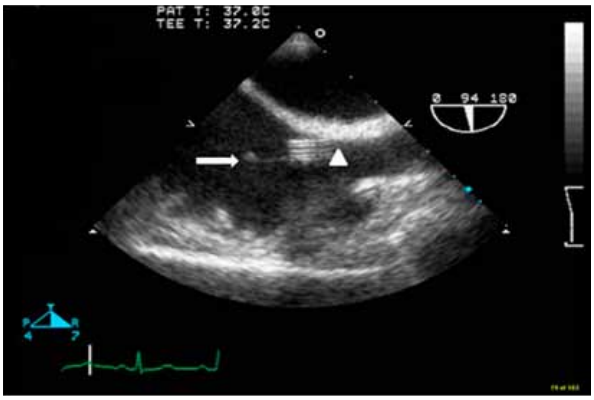

Figure 1. This transesophageal echocardiogram in the longitudinal plane shows the thrombus (arrow) attached to the indwelling venous catheter (arrowhead).

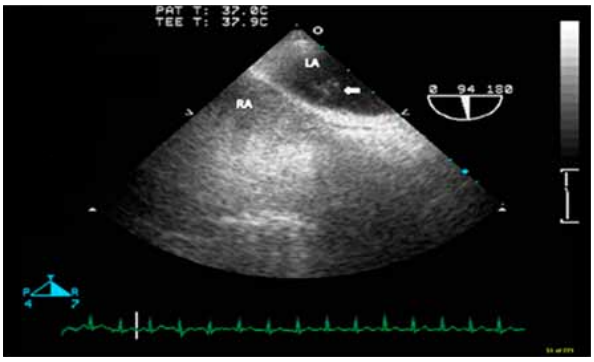

Figure 2. This transesophageal echocardiogram (with bubble study) in the longitudinal plane shows complete opacification of the right atrium (RA) and the passage of a cloud of bubbles (arrow) from the right atrium (RA) to the left atrium (LA), indicating a patent foramen ovale.

One potential source of thrombosis in cancer patients is indwelling central venous catheters. Many patients have these in place, as they facilitate the ease of blood draws in addition to providing access for treatment, blood transfusions, and parenteral nutrition.[6,7] Indwelling catheters have long been known to increase the risk for deep venous thrombosis.[8] The mechanism of thrombosis has been thought to be due to vessel injury from line insertion and venous stasis caused by the indwelling central venous catheters.[9] Subsequently, clot and fibrin accumulate around or within these catheters, forming a thrombus. The incidence of upper extremity deep venous thrombosis has been reported to be as high as 66% in patients with indwelling central venous catheters.[7] Although the majority of these thrombi are nonocclusive and asymptomatic, they still have the potential to embolize.

With the common use of indwelling venous catheters, in addition to the relatively high incidence of PFO, it is surprising that only a handful of reported cases have

shown the association between these 2 factors to be the cause of a paradoxical embolism.[10-13] In each incident, the venous thrombus associated with an indwelling catheter as well as the PFO were identified. In our case, we cannot completely rule out the possibility that the cause of the patient's embolic stroke was due to another source, such as her mild aortic atherosclerotic disease. However, the presence of a large mobile clot in the setting of a PFO certainly raises the suspicion that this was the culprit.

Due to the substantial risk of thrombosis associated with the use of indwelling catheters, it is conceivable that the incidence of paradoxical emboli has been under-reported in the literature. Given the widespread use of catheters in cancer patients, clinicians must be aware of this potential complication, and it may be worthwhile to consider screening patients for a PFO prior to catheter insertion. The cost-effectiveness of such an approach is, of course, unproven.

Conclusion

The present case describes a patient with a left hemispheric cerebrovascular accident presumed to be secondary to a paradoxical embolus from an indwelling venous catheter through a PFO. Given the frequency of catheter use and the relatively high incidence of PFO, this complication may be under-reported or under-recognized. Clinicians must consider this possibility in patients with indwelling catheters who present with cryptogenic stroke.

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Review

Embolic Stroke in a Patient With a Patent Foramen Ovale and an Indwelling Catheter

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Ahn and colleagues describe the presentation of a patient with a recent diagnosis of lung cancer who presents with sudden-onset neurologic findings while receiving platinum-based systemic chemotherapy.[1] Imaging work-up ruled out central nervous system metastases but identified the presence of a subacute cerebral infarct, likely embolic in origin. In an intensive effort to identify a potential embolic source, the patient's physicians found both a patent foramen ovale and a Medi-Port–associated thrombus. The patient was subsequently anticoagulated, with improvement in neurologic function.

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This case highlights several important clinical issues. The first issue raised is the clinical significance of arterial events as a complication of cancer and chemotherapy. Cancer-associated thrombosis is increasingly being recognized as a major cause of morbidity and mortality in patients with cancer, particularly those receiving chemotherapy.[2] However, the substantial prevalence of arterial events as a component of cancer-associated thrombosis is less well-recognized. Arterial events that can occur in malignancy include stroke, myocardial infarction, and peripheral arterial embolism. Although less common than venous events such as deep vein thrombosis (DVT) and pulmonary embolism, arterial events have significant clinical consequences. Indeed, in a recent analysis of causes of death in cancer outpatients receiving chemotherapy, arterial and venous events together accounted for 9% of all deaths and represented the second-leading cause of death, after the cancer itself.[3] Disturbingly, arterial events are increasing in frequency. In an analysis of hospitalized cancer patients, rates of arterial events increased by 124%

from 1995 through 2003.[4] Part of this increase may be explained by the increasing thrombogenicity of newer antineoplastic agents. For instance, regimens containing bevacizumab (Avastin, Genentech) are associated with significantly increased risk for arterial events (hazard ratio [HR], 2; 95% confidence interval [CI], 1.1–3.8).[5] High rates of arterial events have been observed in clinical trials of other antiangiogenic agents as well,[6] and this toxicity may therefore be a class effect. Relevant to this case, both lung cancer and the use of platinum-containing regimens are strong risk factors for thrombotic events.[4,7]

A second issue highlighted by this case is the importance of catheter-associated thrombosis. It is well-known that central venous catheter placement increases the risk of thrombosis. Rates in contemporary clinical trials are approximately 5%. In a recent meta-analysis, risk factors predictive of catheter-related thrombosis included the use of peripherally inserted central catheters, history of DVT, subclavian venipuncture insertion technique, and improper positioning of the catheter tip.[8] However, multiple randomized studies have not shown a benefit for thromboprophylaxis of catheter-associated thrombosis,[9] and current guidelines do not recommend prophylaxis.[10] It is important, however, to recognize the possibility that a central catheter may be a potential source for embolism or for an extended upper extremity or neck DVT.

Finally, this case points to the importance of a diligent clinical work-up in cryptogenic stroke. The advent of newer echocardiographic procedures has allowed us to begin to recognize the high clinical prevalence (up to one-fourth of unselected patients) of patent foramen ovale (PFO) in the general population. Paradoxical embolus must therefore be considered in the differential diagnosis in patients with malignancy and cryptogenic stroke. If a PFO is diagnosed, it is important to identify an embolic source because it may impact the type and duration of anticoagulation.

Can thrombotic events in cancer outpatients be prevented? This question is the focus of several recent and ongoing clinical trials.[11] Current guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend outpatient thromboprophylaxis only for high-risk myeloma patients receiving regimens containing thalidomide or lenalidomide (Revlimid, Celgene). As this case illustrates, however, patients with common solid tumors, such as lung cancer, are at high risk for potentially devastating thrombotic events. A recently validated predictive risk assessment model uses 5 simple clinical and laboratory variables (site of cancer, hemoglobin, platelet counts, leukocyte counts, and body mass index) and helps identify cancer outpatients at high risk for venous thromboembolic events.[7,12,13] Such approaches to risk stratification coupled with ongoing studies of prophylaxis will hopefully allow clinicians to target thromboprophylaxis to appropriate cancer patients and reduce the burden of thrombotic events for patients with cancer.

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