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Case 29-2014: A 60-Year-Old Woman with Syncope

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PRESENTATION OF CASE

Dr. David Curley (Emergency Medicine): A 60-year-old woman was seen in the emergency department at this hospital after a syncopal episode.

The patient had been well until the day of admission, when light-headedness and dyspnea suddenly developed while she was walking with her husband. The dyspnea improved rapidly with rest, but when she attempted to walk again, she lost consciousness and was lowered to the ground by her husband. She rapidly regained consciousness, and her husband called emergency medical services. On evaluation by paramedical personnel, the oxygen saturation was 71% while she was breathing ambient air and increased to 99% while she was breathing oxygen through a nonrebreather face mask. She was brought to the emergency department at this hospital by ambulance.

On evaluation, the patient reported feeling well, with no shortness of breath, chest pain, light-headedness, dizziness, abdominal pain, nausea, vomiting, or diarrhea; she had had no similar episodes in the past. She reported having a transient episode of cramping in the left calf on the morning of admission that had resolved spontaneously. She had no other notable information in her medical history. She took no medications and had no known allergies. She lived with her husband, had no children, and was a retired health care worker. She did not smoke, drink alcohol, or use illicit drugs. She had traveled approximately 2 weeks earlier by airplane for 4 hours. Her father had died of a stroke at the age of 58 years, and her mother had hypertension, atrial fibrillation, and heart failure. There was no other family history of thrombotic or bleeding events or sudden death.

On examination, the patient appeared well and was not in distress. The blood pressure was 121/81 mm Hg, the pulse 77 beats per minute, the respiratory rate 24 breaths per minute, and the oxygen saturation 88% while she was breathing ambient air and 98% while she was breathing oxygen through a nasal cannula at a rate of 6 liters per minute; the temperature was normal. The weight was 104.6 kg, and the abdomen was obese; the remainder of the examination was normal. An electrocardiogram showed normal sinus rhythm, at a rate of 74 beats per minute, as well as incomplete right bundle-branch block, diffuse submillimeter ST-segment depressions, and T-wave inversions. The platelet count was 120,000 per cubic millimeter (reference range, 150,000 to 400,000), the blood level of carbon dioxide was 20.9

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mmol per liter (reference range, 23.0 to 31.9), and the level of D-dimer was greater than 10,000 ng per milliliter (reference value, <500). The hematocrit, hemoglobin level, total white-cell count, anion gap, and results of tests of coagulation and renal function were normal, as were blood levels of glucose, phosphorus, magnesium, other electrolytes, calcium, troponin T, and N-terminal pro–B-type natriuretic peptide.

Diagnostic procedures were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Christopher Kabrhel: I am aware of the diagnosis. The key features of this case are the sudden onset of symptoms, the hypoxemia, and the normal results of the lung examination. Sudden dyspnea and syncope can be caused by a number of processes, such as cardiac ischemia, dysrhythmia, pneumothorax, pericardial tamponade, and pulmonary embolism. Hypoxemia can be explained by bronchospasm, acute pulmonary edema due to cardiac ischemia, and aspiration of gastric contents (in a patient with impaired consciousness). However, the normal results of the lung examination argue against these possibilities. Of all the diagnoses listed, only pulmonary embolism is associated with the constellation of findings in this patient.

The ST-segment and T-wave changes that were seen on the patient's electrocardiogram are not specific for acute myocardial infarction, but the incomplete right bundle-branch block is consistent with right-sided heart strain, which also supports the diagnosis of pulmonary embolism. In addition, the positive D-dimer test, with a result above the upper limit of detection of the assay in an otherwise healthy patient, increases the probability of venous thromboembolism.

Given that a pulmonary embolism is the most likely diagnosis in this patient, I recommend a focused cardiac ultrasound (FOCUS) examination at the bedside to assess right-sided heart function and to rule out a pericardial effusion. I also recommend computed tomographic (CT) pulmonary angiography to confirm the diagnosis of pulmonary embolism.

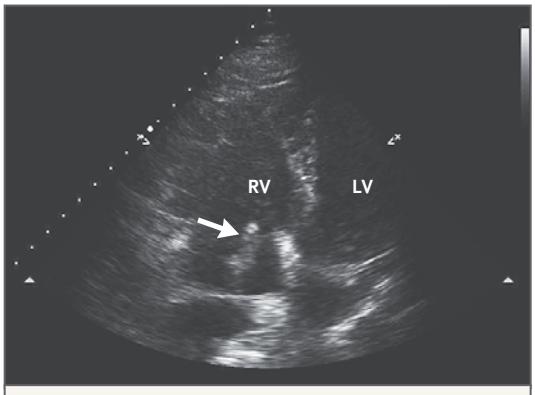

Figure 1. Focused Cardiac Ultrasound Image.
An image that was obtained during a focused cardiac ultrasound examination, performed at the bedside in the emergency department, shows a dilated right ventricle and echogenic material in the right atrium (arrow), findings that are suggestive of thrombus or a mass. LV denotes left ventricle, and RV right ventricle.

FOCUSED CARDIAC ULTRASOUND EXAMINATION

Dr. Joshua S. Rempell: Shortly after this patient presented to the emergency department, a FOCUS examination was performed. A FOCUS examination, also referred to as clinician-performed ultrasonography or point-of-care ultrasonography, provides time-sensitive information that may narrow the differential diagnosis, inform resuscitation strategies, and guide treatment of patients with cardiovascular disease. The purpose of a FOCUS examination is to look for any evidence of pericardial effusion, assess global cardiac function and relative chamber size, and guide emergency procedures. A FOCUS examination is intended to serve as a complement to comprehensive echocardiography[1] and is now considered an essential part of training in emergency medicine.[2,3]

In this case, the apical four-chamber view showed no pericardial effusion, and left ventricular function was preserved. There was a dilated right ventricle (ratio of the size of the right ventricle to the size of the left ventricle, >1.0) and hypokinesis of the right ventricular wall, findings that are consistent with right-sided heart strain. Furthermore, there was akinesis of the free wall and base of the right ventricle but the apex was spared; this distinctive echocardiographic finding, known as McConnell's sign, is not pathognomonic but is highly suggestive of acute pulmonary embolism.[3,4] A mobile echogenic structure in the right atrium raised concern about thrombus or a mass (Fig. 1); this finding requires further evaluation with comprehensive echocardiography. Overall, the findings of the FOCUS examination are consistent with acute pulmonary embolism.

OTHER IMAGING STUDIES

Dr. Laura L. Avery: While the patient was in the emergency department, CT performed according to a pulmonary-embolism protocol revealed pulmonary arterial filling defects within all lobes, extending distally from the segmental arteries; these findings are consistent with extensive pulmonary emboli (Fig. 2). Evaluation of the heart revealed asymmetric dilatation of the right ventricle that was most likely related to right-sided heart strain (Fig. 2). The injection of high-density contrast material in the superior vena cava and right atrium created a marked streak artifact at the level of the right atrium. CT venography of the legs revealed a deep venous thrombosis in the left leg that extended from the popliteal vein to the mid-femoral vein.

CLOT IN TRANSIT

Dr. Kabrhel: Although the vast majority of cases of pulmonary embolism are due to thromboemboli, the differential diagnosis includes embolism of tumor, foreign material, fat, or air. In this patient, the filling defects on CT pulmonary angiography and the presence of residual thrombus on CT venography confirm the diagnosis of pulmonary thromboembolism. The FOCUS examination also revealed a mobile echogenic mass in the right atrium. This finding could represent cancer or infection, but in a patient with acute pulmonary embolism, the most likely cause is residual thrombus in the right atrium, or "clot in transit."

Clot in transit is a dangerous manifestation of pulmonary embolism that is seen in approximately 4% of cases, although this may be an underestimate.[5,6] The mortality associated with pulmonary embolism with clot in transit is high (27 to 45%), with nearly all deaths occurring in the first 24 hours, so rapid and aggressive treatment is essential.[5]

CLINICAL DIAGNOSIS

Acute massive pulmonary embolism.

DR. CHRISTOPHER KABRHEL'S DIAGNOSIS

Acute massive pulmonary embolism with clot in transit in the right atrium and residual deep venous thrombosis.

MANAGEMENT

Dr. Kabrhel: Initially, this patient should receive therapeutic anticoagulation with heparin, though with clot in transit, anticoagulation alone is unlikely to be sufficient because it is associated with a higher mortality (38%) than thrombolysis or surgery.[5] Given that an invasive procedure will probably be required and the effects of anticoagulation may need to be reversed, I would choose intravenous heparin over low-molecular-weight heparin.

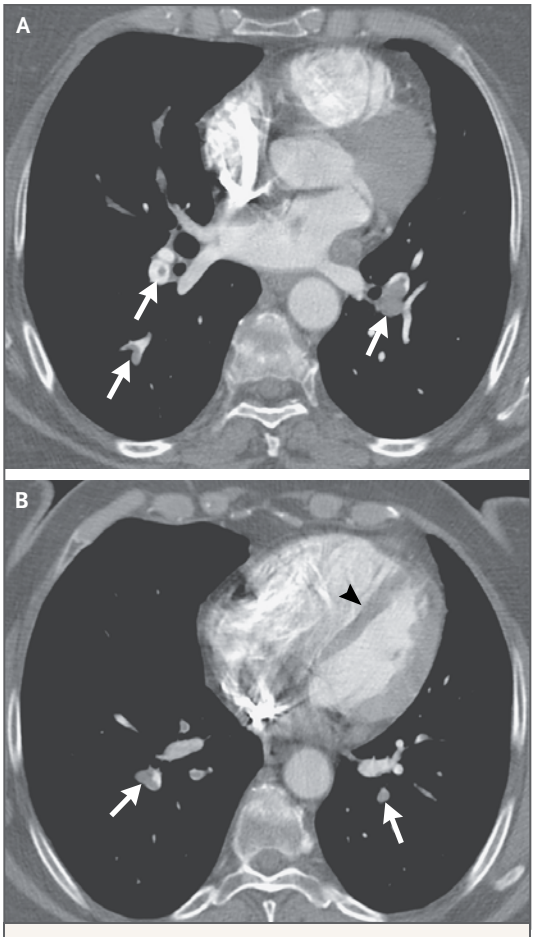

Figure 2. CT Scan of the Chest.
Axial images from contrast-enhanced CT, which was performed according to a pulmonary-embolism protocol, show multiple filling defects in pulmonary arteries (Panels A and B, arrows), findings that are consistent with extensive pulmonary emboli. Evaluation of the heart reveals enlargement of the right ventricle and slight leftward deviation of the interventricular septum (Panel B, arrowhead), findings suggestive of right-sided heart strain.

In addition to anticoagulation, there are several other therapeutic options to consider, including systemic thrombolysis, catheter-directed thrombolysis, aspiration thrombectomy, and surgical thrombectomy. Unfortunately, there are limited data comparing these methods for the treatment of severe pulmonary embolism, and there are even fewer data to guide decision making for the treatment of suspected clot in transit.

PULMONARY EMBOLISM RESPONSE TEAM

Given the complex decision making required in the treatment of this patient, we activated a multidisciplinary rapid-response team, the Pulmonary Embolism Response Team (PERT), comprising experts in cardiology, cardiac surgery, echocardiography, emergency medicine, hematology, pulmonary medicine, critical care, and vascular medicine. The team provides coordinated, real-time consultation with the use of online meeting software. When the timing is critical, the ability to rapidly decide on a treatment plan and mobilize the necessary resources to enact that plan is extremely helpful.

THROMBOLYSIS

We considered administering systemic thrombolysis with intravenous tissue plasminogen activator (t-PA) in this patient. In cases of massive, hemodynamically unstable pulmonary embolism and in the presence of clot in transit, systemic thrombolysis is associated with improved survival, as compared with anticoagulation alone.[5,7] In this case, however, the relatively high risk of major hemorrhage and intracranial hemorrhage tempered our enthusiasm for this approach.[8] If this patient's condition had been hemodynamically unstable, I would have recommended immediate thrombolysis with intravenous t-PA.

Should this patient receive catheter-directed thrombolysis? Thrombolytic therapy can be delivered locally through a catheter inserted into a pulmonary artery. The main advantage of a catheter-directed approach is that a low dose of the thrombolytic agent is typically used.[9] However, in this patient with suspected clot in transit, passing a catheter through the right atrium is risky and could disrupt the clot. Furthermore, administering t-PA in the pulmonary arteries would do little to dissolve the clot in the patient's right atrium. The catheter could be placed in the vena cava, but then the t-PA would flow through a hyperdynamic heart and preferentially into nonoccluded pulmonary arteries, with a reduced dose reaching the clot.

THROMBECTOMY

Aspiration thrombectomy is a relatively new technique that allows clinicians to remove a large volume of thrombus from the right side of the heart or the proximal pulmonary artery. This procedure requires a venotomy and a perfusion team, but it is less invasive than an open surgical thrombectomy. Although there is a paucity of data describing its use in patients with a pulmonary embolism and clot in transit, the procedure is typically well tolerated. A major risk of this approach is that aspiration can fragment a fragile clot and lead to further embolization. In a patient with a patent foramen ovale, a fragmented clot could release emboli into the systemic circulation; therefore, it is important that we rule out a patent foramen ovale in this patient, especially given the high likelihood of elevated right-sided pressures.

Open surgical thrombectomy allows for rapid removal of clots from both the pulmonary arteries and the right side of the heart. The procedure requires a median sternotomy and cardiopulmonary bypass, but improvements in technique and patient selection have greatly increased survival over the past two decades.[10,11] If surgical thrombectomy is performed in this patient, I estimate that the likelihood of survival is greater than 90%. An additional advantage is the ability to repair a patent foramen ovale or septal defect, if present.

After discussing this patient's case, we decided that the best option would be either aspiration thrombectomy or open surgical thrombectomy, depending on the results of comprehensive echocardiography to assess cardiac function and rule out the presence of a patent foramen ovale. We recommended that the patient be given intravenous heparin while she was awaiting the procedure, and if her condition became hemodynamically unstable, that she immediately be given intravenous t-PA.

ECHOCARDIOGRAPHY

Dr. David M. Dudzinski: Transthoracic echocardiography was performed in the emergency department about 15 minutes after the bedside FOCUS examination. The goal of comprehensive transthoracic echocardiography is to confirm the findings of bedside ultrasonography and obtain echo-

cardiographic measurements in order to assess hemodynamic status and right ventricular function. Such information is helpful in gauging the prognosis and guiding therapy in patients with pulmonary embolism. Use of various echocardiographic views may also provide more information about the mobile mass.

Transthoracic echocardiography revealed normal left ventricular size and function and ruled out pericardial effusion. The right ventricle appeared mildly dilated, with impaired overall systolic function; the contractility at the apex was not impaired as compared with the contractility at the base, where marked local systolic dysfunction was noted. The ventricular septal geometry and atrial septal geometry suggested volume overload of the right ventricle and right atrium, respectively. Tricuspid regurgitation was moderate, and the right ventricular systolic pressure was estimated to be 46 mm Hg. These features collectively suggest that the patient has right ventricular dysfunction as a result of the hemodynamic insult and represent a severe form of pulmonary embolism.

A highly mobile, serpiginous mass in the right atrium raised concern about the possibility of clot in transit. The echotexture, shape, and motion of the mass were most consistent with thrombus arising from a deep vein (Fig. 3; and Videos 1 and 2, available with the full text of this article at NEJM.org). The total length of the mass was estimated to be 8 cm. On multiple images, the mass was localized in the right atrium; although there

Videos are available at NEJM.org

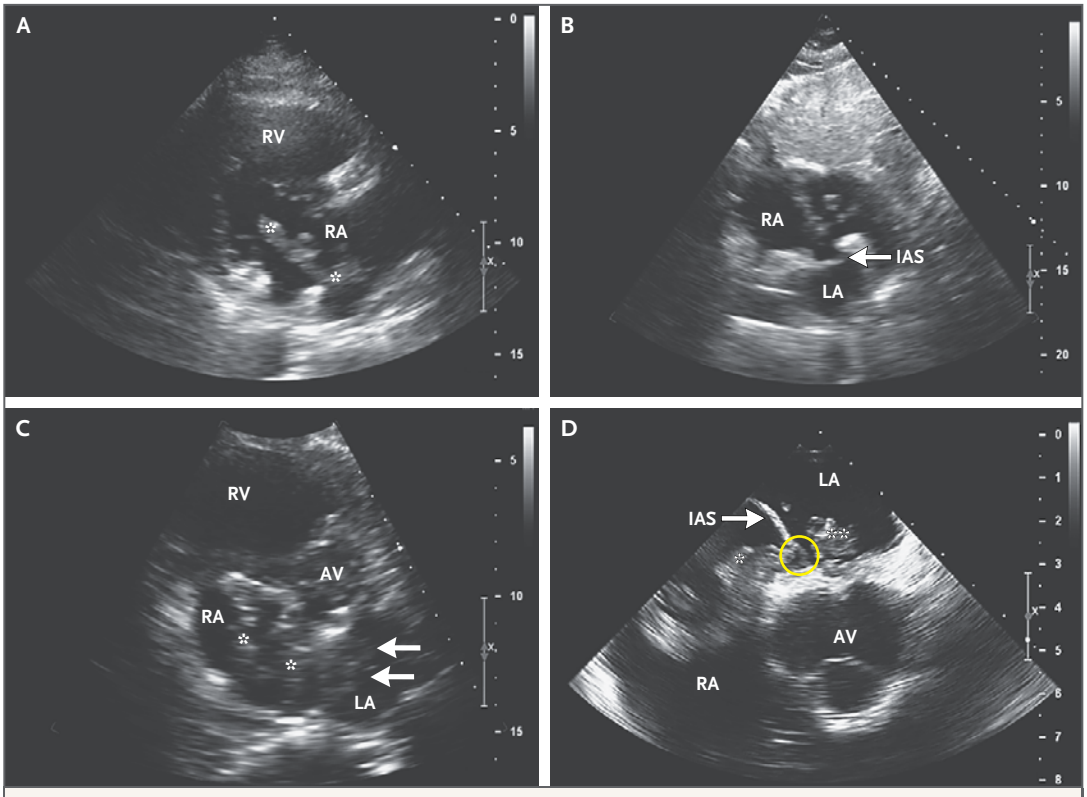

Figure 3. Echocardiographic Images.

A transthoracic echocardiographic image obtained in the right ventricular inflow view at end diastole shows a cylindrical echogenic mass in the right atrium (Panel A, asterisks [at ends of mass]). An image obtained in the subcostal view shows an echogenic mass in the right atrium, as well as the interatrial septum (Panel B, arrow) and left atrium; the right atrium appears to be larger than the left atrium. An image obtained in the parasternal short-axis view at the level of the aortic valve shows an echogenic mass in the right atrium (Panel C, asterisks); however, there are also increased echodensities along the left atrial side of the interatrial septum (Panel C, arrows). A transesophageal echocardiogram, obtained to further evaluate these findings, shows a serpiginous echogenic mass in the right atrium (seen on transthoracic echocardiography) and extending through to the left atrium (Panel D, asterisks); the location suggests that the interatrial communication occurs through a patent foramen ovale (circle). AV denotes aortic valve, IAS interatrial septum, LA left atrium, and RA right atrium.

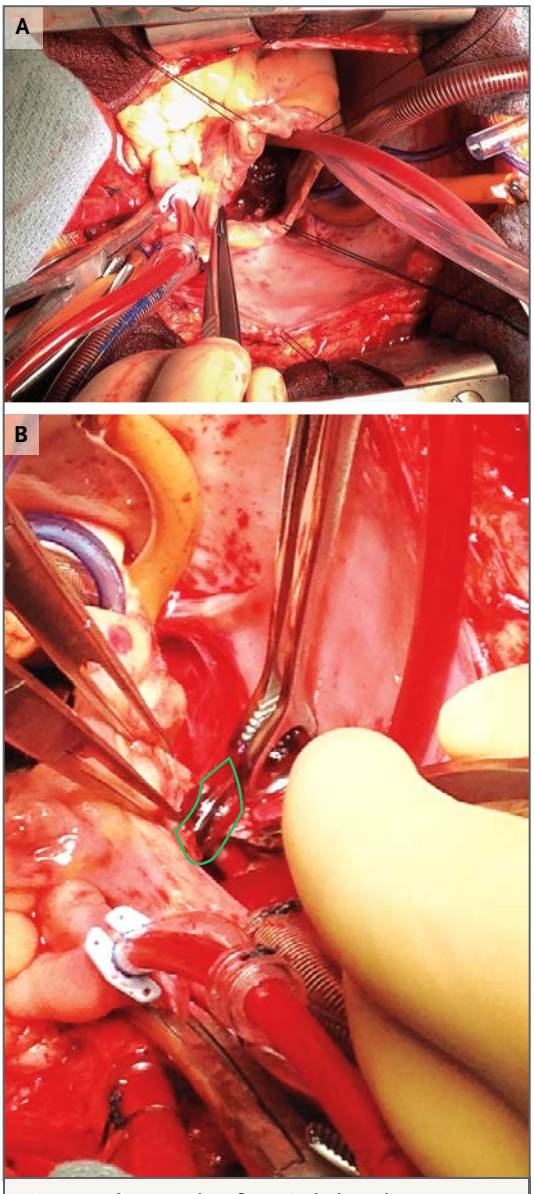

Figure 4. Photographs of Surgical Thrombectomy.
The patient underwent emergency surgical thrombectomy to remove the clot. During the procedure, the thrombus was visualized in both the right atrium (Panel A) and the left atrium (Panel B, outlined in green), located in the patent foramen ovale. The thrombus was extracted, and the patent foramen ovale was closed. (Photographs courtesy of Dr. Serguei Melnitchouk.)

was intermittent prolapse of a portion of the mass into the right ventricle during diastole, it remained anchored in the right atrium. Possible attachment points included the eustachian valve and the interatrial septum. Additional mobile echodensities noted in the left atrium (Fig. 3 and Video 3) raised the possibility that the thrombus reached the left heart.

The concern about embolization of the clot in transit from the right side of the heart to the left side of the heart was shared with members of the PERT during a conference call to discuss therapeutic strategy. We elected to perform urgent transesophageal echocardiography to help inform the ultimate treatment decision. Given the potential for hemodynamic compromise in this patient, transesophageal echocardiography was performed in the cardiac catheterization laboratory, with sedation provided by the cardiac anesthesia service. Transesophageal echocardiography confirmed embolization of the mass through a patent foramen ovale (Fig. 3 and Videos 4 and 5), thus accounting for the mobile echodensities in the left atrium, as well as the observed anchoring of the mass in the right atrium. Other findings, including right ventricular dilatation, right ventricular hypokinesis, and right ventricular and right atrial volume overload, were similar to those seen on transthoracic echocardiography.

Dr. Eric Rosenberg (Pathology): Dr. Narayan, would you tell us what happened next?

Dr. Rajeev L. Narayan (Vascular Medicine and Intervention): Since a patent foramen ovale was found on transesophageal echocardiography, we decided against the aspiration thrombectomy because of concern about potential fragmentation of the thrombus and paradoxical embolization. The patient was taken to the operating room for emergency surgical thrombectomy, which involves a median sternotomy and cardiopulmonary bypass with aortic cross-clamping. During the procedure, the thrombus was visualized in both the right atrium and the left atrium, located in the patent foramen ovale. The thrombus was extracted, and the patent foramen ovale was closed (Fig. 4). The surgery was uneventful, and the patient was neurologically intact on awakening, without clinical evidence of cerebrovascular embolization. Anticoagulation with heparin was restarted, with a subsequent transition to warfarin; the planned target range for the international normalized ratio was 2 to 3.

The patient's postoperative course was complicated by episodes of atrial fibrillation, which were controlled with beta-blockers and amiodarone. Noninvasive duplex ultrasonography of the venous system in the legs revealed occlusive

thrombus throughout the left femoral vein, popliteal vein, and small saphenous vein. The patient underwent successful implantation of an inferior vena cava filter and was discharged on hospital day 8, with arrangements for follow-up with the vascular medicine, cardiothoracic surgery, and hematology services, as well as with anticoagulation management services and primary care.

At the follow-up visits, the patient was well, without evidence of recurring venous thromboembolism. She remained in sinus rhythm and had good exercise capacity, and the warfarin therapy did not have unacceptable side effects. She wears compression stockings on both legs. We discontinued amiodarone therapy and made plans for removal of the inferior vena cava filter.

LONG-TERM MANAGEMENT

Dr. Ido Weinberg: There are several questions to consider when developing a long-term management plan in this case. First, how long should the patient receive anticoagulation? In general, the duration of anticoagulation should be determined on the basis of the underlying cause of pulmonary embolism. If this case of pulmonary embolism was a provoked event, the patient should receive anticoagulation for a relatively short period.[12,13] However, current guidelines suggest lifelong treatment in patients who have had unprovoked thrombosis.[13] Although this patient has several risk factors for pulmonary embolism, including being overweight and having recently traveled by air, I consider this an unprovoked event[14-16] and therefore recommend lifelong anticoagulation.

Given that the pulmonary embolism was most likely unprovoked in this patient, does she need to be screened for an underlying cancer? If cancer is found, that would affect both the choice of anticoagulant and the risk of recurrence.[17] Routine screening according to the patient's age, symptoms, and sex is usually advocated, but a more extensive evaluation is generally not warranted.[18-20]

Finally, is there any way to predict whether this patient will have a recurrence of deep venous thrombosis or pulmonary embolism? For patients who have had an unprovoked event and who are reluctant to take anticoagulants on a lifelong basis, the risk of recurrence can be predicted by measuring the D-dimer level while the anticoagulant is withheld.[21] Deep venous thrombosis and pulmonary embolism tend to recur in the same form as the initial clinical manifestation[22]; thus, this patient is at particular risk for recurrent pulmonary embolism, a factor that should also be considered before discontinuing anticoagulation.

Dr. David F.M. Brown (Emergency Medicine): Was the presence of a patent foramen ovale actually beneficial in this patient, because it trapped a clot that might otherwise have passed into the pulmonary vasculature and caused sudden death?

Dr. Kabrhel: I suspect that the presence of a patent foramen ovale probably did help this patient. Embolization of the rest of the thrombus, which was 8 cm long and about 1 cm wide, would have certainly resulted in hemodynamic instability, if not in sudden death.

Dr. James A. Gordon (Emergency Medicine): What is the role of extracorporeal membrane oxygenation (ECMO) in patients with pulmonary embolism?

Dr. Kabrhel: We are increasingly using ECMO in the care of patients with hemodynamically unstable pulmonary embolism, mostly as a bridge to thrombectomy or thrombolysis.

Dr. Eric Nadel (Emergency Medicine): I imagine that the development and maintenance of the PERT requires a considerable investment of resources. Is this approach cost-effective?

Dr. Kabrhel: Although there are no data yet to determine whether this is a cost-effective approach, we think that it probably saved this woman's life and may have prevented cardiopulmonary disability after pulmonary embolism.

FINAL DIAGNOSIS

Acute massive pulmonary embolism with clot in transit through the right atrium and residual deep venous thrombosis.

Dr. Kabrhel reports receiving consulting fees from Diagnostica Stago and grant support to his institution from Diagnostica Stago and Siemens Healthcare; Dr. Dudzinski, consulting fees from Sanofi and Advantage Health Care; and Dr. Weinberg, consulting fees from VIVA Physicians. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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