Simultaneous Systemic and Pulmonary Thromboembolism in the Absence of an Obvious Intracardiac Shunt

Ribal S. Darwish, MD
Timothy B. Gilbert, MD, MBA, FACC
Anila S. Bhatti, MD
Mary K. Ferguson, RDCS
Brenda G. Fahy, MD, FCCM

The simultaneous occurrence of pulmonary and systemic thromboembolism typically results from an identifiable intracardiac shunt. In the following case, an otherwise healthy woman without known risk factors for hypercoagulability presented with pulmonary embolism and nearly simultaneous thromboembolism to both lower extremities. This case was unusual because repeated transesophageal echocardiographs (TEEs) did not reveal an obvious intracardiac defect, and helical computed tomography (CT) scan of the chest did not detect an intrapulmonary shunt. This article reviews the etiology, diagnosis, and management of paradoxical embolus and pulmonary embolism. Management of hypercoagulable state also is briefly discussed.

CASE PRESENTATION

Initial Presentation

A 56-year-old woman without significant past medical history presented to the emergency department with a chief complaint of weakness of both lower extremities that had been increasing over the previous 3 days. On admission, her vital signs were: heart rate, 128 bpm; blood pressure, 120–130/70–80 mm Hg (equal in both arms); respiratory rate, 18 breaths/min; temperature 96.3°F (35.2°C); and room air Spo_2, 84%. She was awake and alert but complained of mild respiratory distress. There was no jugular venous distention or carotid bruits, and findings on auscultation of the heart and lungs were normal. The abdomen was soft and nontender with no pulsatile masses or distention. Although pulses were strong and equal in the upper extremities, there were no palpable pulses below the femoral arteries bilaterally.

Evaluation and Initial Management

An electrocardiogram revealed sinus tachycardia, a slightly prolonged QT interval, and episodic supraventricular tachycardia. Arterial blood gas values (on 4 L/min oxygen via nasal cannula) revealed a pH of 7.52, $PaCO_2$ of 27 mm Hg, and PaO_2 of 146 mm Hg. The leukocyte count was $21.3 \times 10^3/mm^3$, hemoglobin was 12.3 g/dL, and platelet count was $35 \times 10^3/mm^3$. Baseline values prior to admission were unknown. Electrolytes, renal and liver function, prothrombin time, and activated partial thromboplastin time (aPTT) were normal.

Duplex sonography of the lower extremities showed bilateral superficial femoral arterial thrombus with absent flow below the popliteal artery. Furthermore, the venous-phase duplex showed left superficial femoral vein thrombus with inferior extension. Urgent ventilation/perfusion scanning was considered but was not performed due to the patient's severe hemodynamic and respiratory instability.

After initial bolus administration, an infusion of heparin was started intravenously. Over the next 12 hours, a line of demarcation developed at the level of the knees with loss of motor and sensory function. Emergency intra-arterial thrombolysis with streptokinase by interventional radiology was attempted without apparent

Dr. Darwish is an assistant professor of anesthesiology and critical care medicine, Dr. Gilbert is an associate professor of anesthesiology and medicine (cardiology), Dr. Bhatti is a senior resident, and Dr. Fahy is an associate professor of anesthesiology; all are at the University of Maryland School of Medicine, Baltimore, MD. Ms. Ferguson is a supervisor of intraoperative echocardiography, University of Maryland Health System, Baltimore, MD.

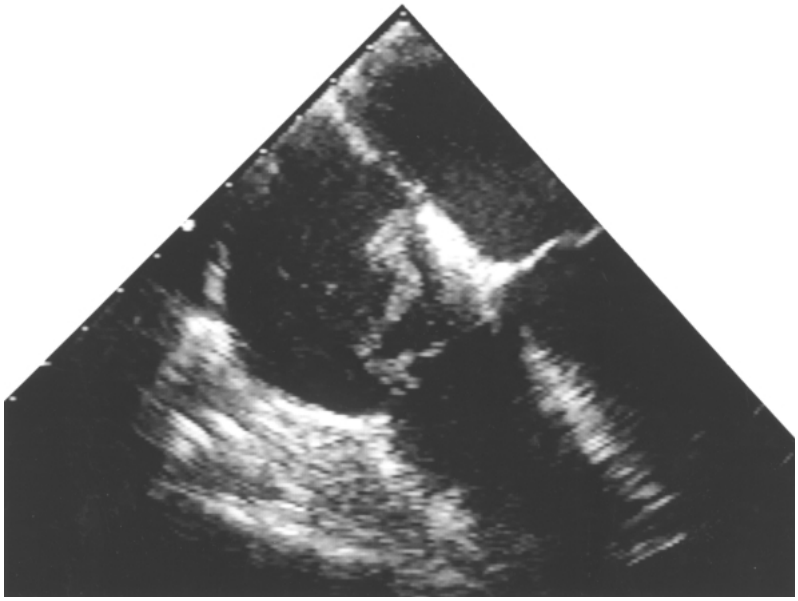

Figure 1. Transesophageal echocardiograph of the case patient on hospital day 1. A large, serpiginous thrombus is noted in the right atrium, lateral to the intra-atrial septum and superior to the septal leaflet of the tricuspid valve.

success. Because of the necessity for immediate open vascular surgical interventions on both legs and the concern for perioperative hemorrhage, systemic thrombolysis was not attempted.

Clinical Course

On the first hospital day, bilateral lower extremity thrombectomies and fasciotomies were performed under general anesthesia in the operating room. Intraoperatively, severe hypotension occurred, necessitating volume resuscitation, invasive monitoring, and inotropic support. After placement of a pulmonary artery catheter (PAC), pulmonary and right atrial hypertension (pulmonary artery pressure = 64/32 mm Hg, central venous pressure = 19 mm Hg) were noted. Due to the high clinical suspicion for a pulmonary embolism, intraoperative TEE was obtained, which demonstrated a left ventricular ejection fraction of approximately 60% and a 5- to 6-cm dilated right atrium. A large serpiginous echodensity was seen at the right atrium/inferior vena caval junction that prolapsed through the tricuspid valve (**Figure 1**). However, no thrombus was seen in the left atrium or proximal pulmonary vasculature, despite careful examination of both the chamber and vessels. Furthermore, there were no patent foramen ovale or atrial or ventricular septal defects.

Anticoagulation was maintained with an infusion of heparin, with a goal of an aPTT of 60 to 80 sec. A repeat TEE was obtained on the third hospital day because of an episode of hemodynamic instability. A thrombus was now clearly identified in the left atrium (**Figure 2**), but again there was no evidence of an intracardiac shunt. Ultimately, bilateral above-knee amputations were required on the fourth hospital day. On the eleventh hospital day, a suboptimal quality helical CT of the chest with intravenous contrast noted patchy areas of a possible pulmonary infarction in the periphery of both lungs, but there was no evidence of a pulmonary arteriovenous malformation or large central/segmental emboli. Finally, a diagnosis of pulmonary infarction secondary to pulmonary embolism was made.

Hematologic workup for hypercoagulability included: protein C, 81% (normal, 70%–130%); protein S, 69% (normal, 70%–150%); and antithrombin III, 75% (normal, 80%–120%). Neither the factor V Leiden mutation nor antiphospholipid antibodies were detected. Ultimately, the patient recovered and was discharged on long-term warfarin therapy to a rehabilitation facility.

DISCUSSION

Paradoxical Embolus

Paradoxical embolus should be considered in any patient with an arterial embolus in the absence of an intracardiac or proximal arterial source, particularly if multiple organs are involved.[1] Indeed, "unconventional" causes of peripheral emboli should be investigated in any patient without risk factors for left-sided heart thrombus.[2,3] Atypical presentations of pulmonary embolism are certainly not uncommon.[4] Despite these provisos, paradoxical embolus continues to be under- or misdiagnosed.[5] In general, a diagnosis of paradoxical pulmonary embolus (as proposed by Johnson) is based on the presence of arterial embolism, an intracardiac

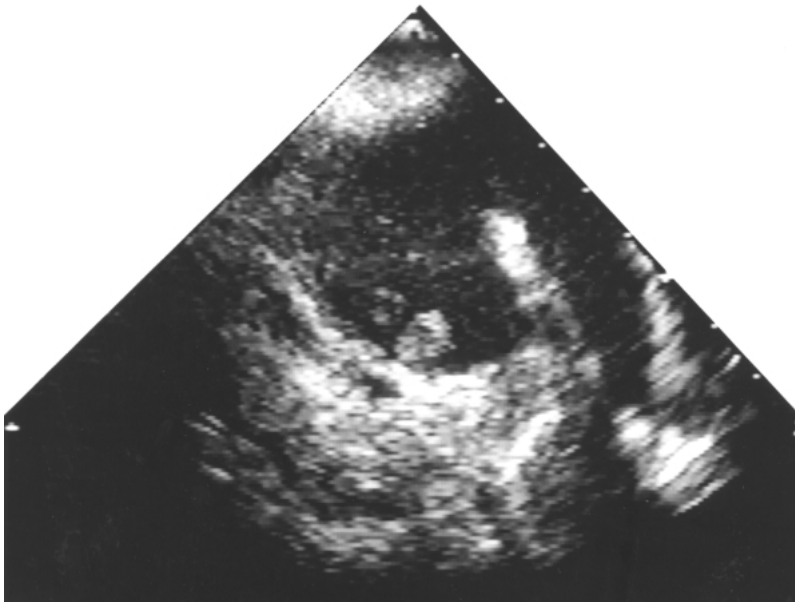

Figure 2. Transesophageal echocardiograph of the case patient on hospital day 3. A new left atrial thrombus is noted, inferior to the left atrial appendage and superior to the posteromedial leaflet of the mitral valve.

defect with right-to-left shunt, and venous thrombosis.[6] In the case patient, however, the presence of an intracardiac defect could not be established.

The most common defect associated with paradoxical embolus is a patent foramen ovale, although any intracardiac (or intrapulmonary) defect could be capable of transporting thrombi between the chambers. A patent foramen ovale is not an uncommon anomaly; Thompson and Evans demonstrated the presence of a probe-patent foramen ovale in 6% of 1000 autopsies.[7] The simultaneous occurrence of both a patent foramen ovale and an atrial septal aneurysm even further increases the risk for systemic embolization.[8] Contrast TEE has been considered the gold standard for demonstration of intracardiac defects and right-to-left shunts. In this case, however, repeated contrast TEE failed to demonstrate any obvious intracardiac defect.[9] We hypothesize that the shunt was patent only transiently and possibly was induced by a Valsalva maneuver or as a consequence of occult pulmonary emboli—any of which can elevate right-sided heart pressures relative to the left heart.

The most effective strategy in the diagnosis of paradoxical embolus remains to be determined, although TEE is most commonly utilized. Other diagnostic modalities exist for detecting intracardiac shunts but are less sensitive (eg, cardiac catheterization, oxygen step-up between chambers). TEE is more sensitive for detection of patent foramen ovales (89%)[10] than for intracardiac thrombus (35%)[11] and correlates well with autopsy findings.

Diagnosis of Pulmonary Embolism

Ventilation/perfusion scanning, combined with clinical assessment, only establishes or refutes a diagnosis of pulmonary embolism in a minority of patients[12] and requires specialized equipment and personnel—often off-site from the critically ill patient. Echocardiography is more ideal because it is readily transportable, can differentiate shock states, and sometimes visualize vascular thrombus. However, helical high-resolution CT is evolving to replace angiography as a confirmatory study in this at-risk population.[13] In the case patient, even though no central emboli were noted in the pulmonary vasculature by either echocardiography or helical CT scanning, the indirect evidence for pulmonary embolism was overwhelming: presence of serpiginous clot in a dilated right atrium, pulmonary hypertension, hypoxia, dyspnea, bilateral lower extremity venous thrombosis, and apparent hypercoagulability. Therefore, the diagnosis was based on these findings and a very high clinical suspicion for pulmonary embolism.

The actual insertion and use of a PAC in the setting of an acute pulmonary embolism of any source is controversial owing to its potential for potentiating thrombus on the catheter surface or propagating it during insertion. In the current case, the PAC was removed following its initial measurements and the clinical diagnosis of pulmonary embolism.

Management of Hypercoagulable State

The specific etiology of a hypercoagulable state could not be determined in the case patient.[14]

Although the common thrombophilias were assayed, other coagulation-related mutations (eg, prothrombin G20210A[15]) were not determined in this patient. Generally, heparin-induced thrombocytopenia—and its associated "white-clot" syndrome—is suspected only after the recurrence of thromboemboli; however, in this patient, the platelet count was abnormally low prior to the administration of heparin. Furthermore, heparin-induced thrombocytopenia generally is noted after approximately 5 days of therapy, and more rarely, in shorter periods.[16] Assays for heparin-associated antibodies were not available for this patient.[17] The occurrence of bilateral lower extremity ischemia also suggested Buerger's disease; however, the clinical presentation and angiographic findings did not support significant coexisting arteritis or other vascular disease.[18]

Management of Acute Pulmonary Embolism

Although systemic thrombolytic treatment was avoided in this patient because of the obvious immediate need for surgical interventions, tissue plasminogen activator is an approved agent for treatment of acute pulmonary embolism with significant hemodynamic or respiratory compromise. It is administered as a 100 mg intravenous infusion over 2 hours, followed by heparin administration when the aPTT falls below twice the normal value.[19] In one promising series, early thrombolysis was deemed effective in 57% of patients presenting with massive pulmonary embolism.[20] However, the use of systemic thrombolytics for treatment of pulmonary embolism in other settings (eg, isolated right heart dysfunction, pulmonary hypertension, or recurrences) remains controversial.[21]

CONCLUSION

Paradoxical embolus may account for acute arterial occlusion in the absence of a clear cardiac shunt. The optimal diagnostic method to find temporary intracardiac shunts is yet to be established. **HP**

REFERENCES

1. Islam MA, Khalighi K, Goldstein JE, Raso J. Paradoxical embolism—report of a case involving four organ systems. J Emerg Med 2000;19:31–4.
2. AbuRahma AF, Richmond BK, Robinson PA. Etiology of peripheral arterial thromboembolism in young patients. Am J Surg 1998;176:158–61.
3. Abreu A, Branco L, Bento MJ, et al. [Diagnosis of paradoxical and concomitant pulmonary thromboembolism with transesophageal echocardiography: a clinical case.] [Article in Portugese.] Rev Port Cardiol 2000;19:823–8.
4. Fisher WT, Reilly K, Salluzzo RF, et al. Atypical presentation of pulmonary embolism. Ann Emerg Med 1990;19: 1429–35.
5. Ward R, Jones D, Haponik EF. Paradoxical embolism. An underrecognized problem. Chest 1995;108:549–58.
6. Aburahma AF. Work-up and management of patients with paradoxical emboli. W V Med J 1996;92:260–4.
7. Thompson T, Evans W. Paradoxical embolism. QJM 1930;23:135–50.
8. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345: 1740–6.
9. Travis JA, Fuller SB, Ligush J Jr, et al. Diagnosis and treatment of paradoxical embolus. J Vasc Surg 2001;34: 860–5.
10. Schneider B, Zienkiewicz T, Jansen V, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. Am J Cardiol 1996;77:1202–9.
11. Uchiyama S, Yamazaki M, Iwata M, Maruyama S. [Diagnosis of intracardiac thrombi by various imaging techniques and activation of platelets and coagulation-fibrinolysis in patients with cardioembolic stroke.] [Article in Japanese.] Rinsho Shinkeigaku 1996;36:429–35.
12. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA 1990;263:2753–9.
13. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002; 121:877–905.
14. Lee LC, Shah K. Clinical manifestations of pulmonary embolism. Emerg Med Clin North Am 2001;19:925–42.
15. Gilchrist A, Solomon N, Erickson D, et al. Automated detection of the G20210A prothrombin mutation using the LCx microparticle enzyme immunoassay. Clin Chim Acta 2001;314:249–54.
16. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. Ann Intern Med 2002;136:210–5.
17. Kelton JG. Heparin-induced thrombocytopenia: an overview. Blood Rev 2002;16:77–80.
18. Kurata A, Franke FE, Machinami R, Schulz A. Thromboangiitis obliterans: classic and new morphological features. Virchows Arch 2000;436:59–67.
19. Physicians' desk reference. 57th ed. Montvale (NJ): Medical Economics; 2002. Activase:1393.
20. Tayama E, Ouchida M, Teshima H, et al. Treatment of acute massive/submassive pulmonary embolism. Circ J 2002;66:479–83.
21. Almoosa K. Is thrombolytic therapy effective for pulmonary embolism? Am Fam Physician 2002;65:1097–102.