CLINICAL VIGNETTE

A Life-Threatening Complication of Venous Thromboembolism

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Introduction

Clot-in-transit (CIT), also termed "free-floating right heart thrombi" or "right heart thrombi," is defined as thrombus believed to have embolized from the deep veins, becoming temporarily lodged in the right atrium or right ventricle before reaching its destination in the pulmonary vasculature.[1] It is almost always associated with pulmonary embolism (PE).[2] Of patients with diagnosed PE, CIT has a reported prevalence of 18% in the critical care setting.[3] CIT has been associated with increased morbidity and mortality, with one study suggesting up to 100% mortality rate if left untreated.[2] In the most recent European Society of Cardiology Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism (ESC Guidelines),[4] right heart thrombi are noted as associated with "high early mortality" and may be used in risk-stratification of case severity. Data has largely been obtained from case series, retrospective analyses, and registry data. Here, we build on existing literature by reporting a case report of a patient with high-risk pulmonary embolism with associated CIT. We discuss decision-making in this emergency scenario and provide a review of the literature regarding this rare presentation.

Case Summary

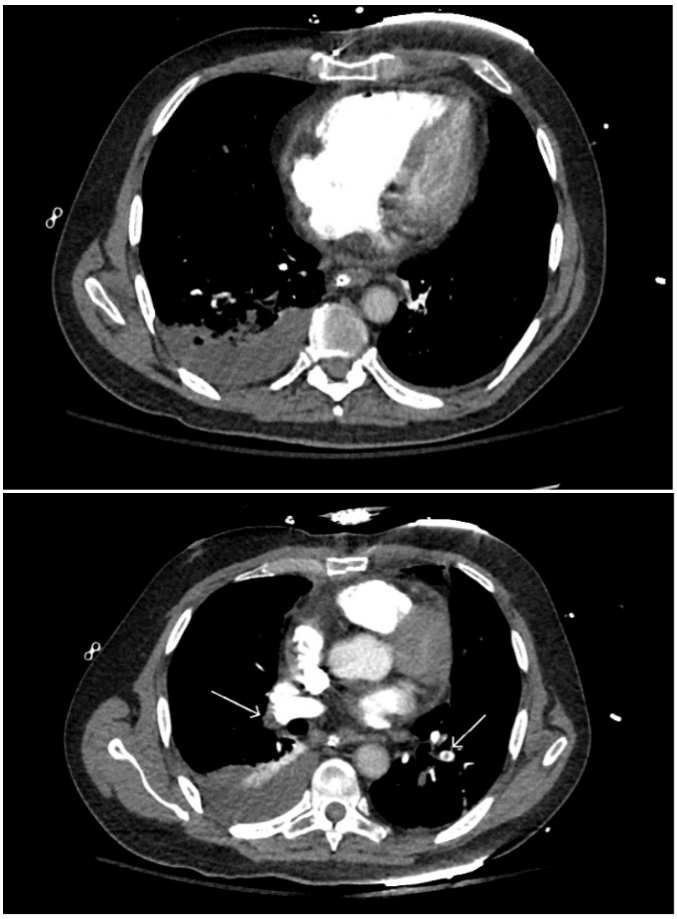
A 67-year-old male with recent left atrial myxoma excision and atrial septal defect repair, suffered out-of-hospital cardiac arrest after calling emergency medical services (EMS) for back pain. EMS secured his airway and performed cardiopulmonary resuscitation for about 25 minutes. Upon arrival, vitals were notable for temperature of 33.4°C, heart rate of 120 bpm, respiratory rate of 28/min, blood pressure of 69/39 mmHg, and oxygen saturation of 100% on mechanical ventilation. On physical exam, he was breathing spontaneously while on the ventilator. He was moving all extremities spontaneously and otherwise had no gross focal neurological deficits. Electrocardiogram revealed sinus tachycardia and rSr' pattern in lead V1.

Computed tomography pulmonary angiography (CTPA) revealed acute bilateral lobar, segmental, and subsegmental pulmonary emboli (PE) and evidence of right heart strain with an RV/LV ratio of 2.0. Peak troponin-I was 2.041 ng/mL and brain natriuretic peptide was 344 pg/mL. Our institutional Pulmonary Embolism Response Team (PERT) was activated. After a review of strict contraindications, intravenous unfractionated heparin was started. Urgent transthoracic echocardiography (TTE) revealed a 3.5cm irregular and mobile echodensity extending across the tricuspid valve from the right atrium to the right ventricle.

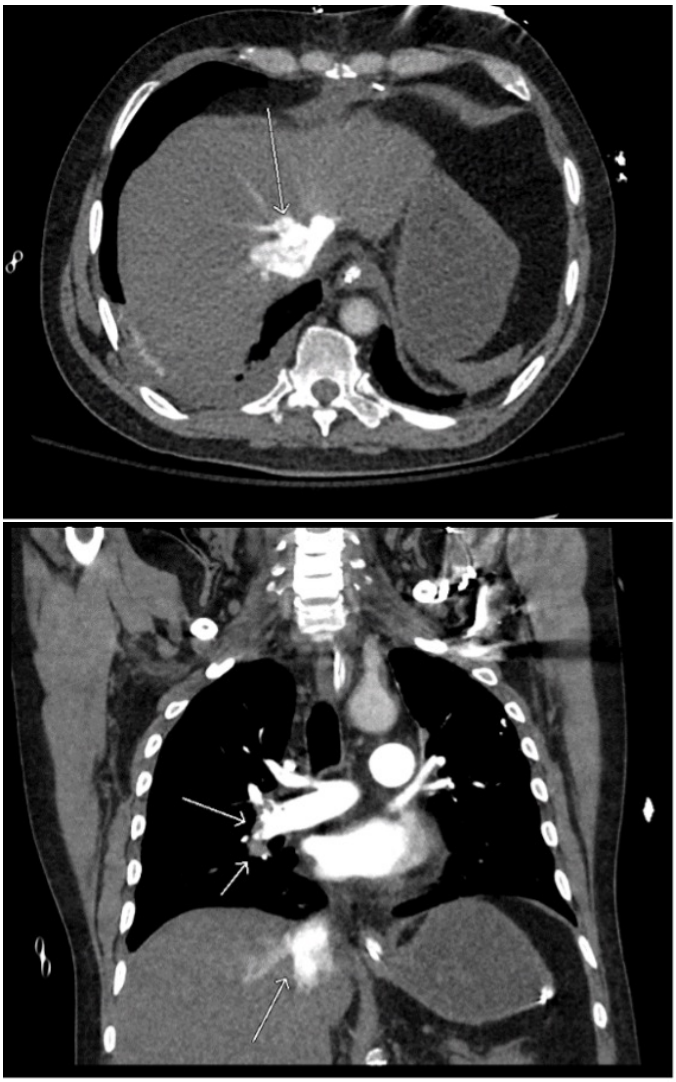
His past medical history also included hypertension and left cerebellar ischemic stroke 3 months prior. In multidisciplinary discussion, it was determined that the patient was a poor candidate for surgical embolectomy or catheter-directed therapies (CDT). The patient began to decompensate, requiring two vasopressors to sustain organ perfusion. Throughout this event, the patient maintained mental status and was able to follow basic commands. Systemic thrombolysis was pursued as the patient clinically deteriorated with no other viable alternative. Given contraindications of recent cardiac surgery, recent ischemic stroke, thrombocytopenia, coagulopathy, and prolonged CPR, half-dose systemic alteplase (50mg) was administered over two hours. The patient had a transient improvement in hemodynamics. This was followed a few hours later by rapid decompensation to the point of requiring five vasopressors and one inotrope to sustain organ perfusion, with waning mental status. It was suspected that clot burden persisted or a recurrent embolic event occurred, leading to acute right ventricular failure and hemodynamic collapse. The decision was made to administer a second half-dose of 50mg systemic alteplase. During infusion, hemodynamics marginally improved. Shortly after completion, the patient again required increasing hemodynamic support. Labs included, a significant drop in hemoglobin and the patient was resuscitated with blood products. Hemodynamic support continued through the patient's intensive care course, with his post-thrombolytic anticoagulation intermittently held when bleeding was suspected.

Two days after initial presentation, his bleeding resolved spontaneously. A repeat TTE showed near-absent CIT and improvement in right ventricular systolic function. The patient's course was further complicated by heparin-induced thrombocytopenia, likely secondary to heparin exposure while on cardiopulmonary bypass during his recent atrial myxoma excision, and likely contributing to his presentation of high-risk pulmonary embolism. The patient was switched to intravenous argatroban, gradually weaned off vasopressor and inotropic support, and extubated in stable condition. He was discharged on rivaroxaban. TTE performed at discharge (ten days after

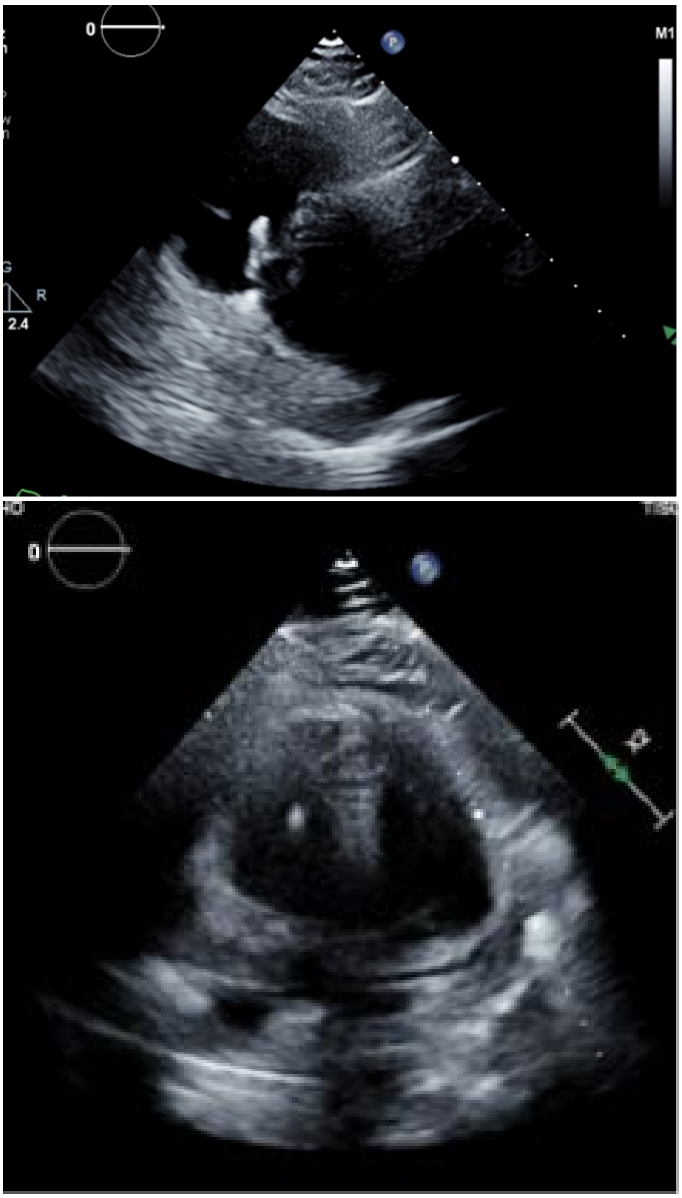
presentation) demonstrated normal right ventricular size and function, normal estimated pulmonary arterial pressure, and no evidence of CIT. At his 3-month follow-up visit, he had no functional limitations and was in good state of health.



Enlarged right ventricle with a ratio to left ventricle about 2.0. Bilateral emboli (arrows).



Hepatic reflux of contrast (arrow). Right interlobar pulmonary artery emboli (arrow) and contrast reflux into hepatic veins.



CIT traversing tricuspid valve in RV inflow view. View of portion of CIT in apical-four-chamber view.

Discussion

Pulmonary embolism is the third leading cause of vascular death worldwide.[5] The current risk-stratification scheme used at our institution derives from the 2019 European Society of Cardiology Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism.[4] High-risk is defined by the presence of obstructive shock, persistent hypotension with a systolic blood pressure (SBP) <90 mmHg for >15 minutes despite resuscitation, or cardiac arrest. The established treatment of choice is systemic thrombolysis. In the face of relative or absolute contraindications to systemic thrombolysis, surgical embolectomy and CDT are alternatives. Multiple factors go into this complex decision-making, however, the clinical significance of CIT is unclear. Prevailing literature indicates an increase in mortality in patients with intermediate-risk PE who are treated with anticoagulation alone, suggesting advanced therapies (particularly thrombolysis) must be considered.[2,3,6] It is more difficult to assess the impact of CIT on outcomes, and whether this should drive clinical decisions, in the high-risk PE population.

Several studies report an association between CIT and increased clinical severity. Torbicki et al.[6] performed a registry analysis comparing patients with CIT (n=42) to those without (n=1071). They found patients with CIT were more hemodynamically compromised at time of diagnosis compared to patients without CIT, with a greater proportion of patients with SBP< 90 mmHg (14% vs 5%, $p<0.05$). Though mortality was increased in the group with CIT, an independent causative effect of CIT on mortality could not be confirmed. They concluded it is unclear whether CIT confers an independent risk of mortality or is solely a marker of adverse outcome. A major limitation was the lack of differentiation into high, intermediate, and low-risk groups.

Cassaza et al.[7] performed a registry analysis of 1275 patients who had echocardiography performed within 48 hours of admission. Patients were risk-stratified in according to ESC Guidelines.[4] CIT was detected in 57 patients (4.5%), and in 16% of high-risk patients. CIT was found in only 3.8% of intermediate-risk and 0.3% of low-risk patients. Within the high-risk group, presence of CIT was associated with lower systolic blood pressure and higher prevalence of cardiac arrest. Comparable observations of clinical deterioration were not found in the intermediate and low risk groups with CIT. The authors concluded that true prevalence of CIT is likely associated with severity of PE, and increased prevalence in high-risk patients may be due to increased pulmonary pressure and decreased cardiac output contributing to stasis in the right heart chambers (Barrios et al. concluded similarly[3]). Like Torbicki et al,[6] they found that the presence of CIT itself was not significantly associated with higher all-cause or PE-related mortality in the high-risk group (though a trend towards worse prognosis was noted). While more frequent use of systemic thrombolysis was noted in high-risk patients with CIT compared to those without, no conclusion regarding optimal treatment could be made.

Another registry-based study involving 138 patients with CIT sought to address the association between PE-related mortality and severity of PE.[8] This group was compared to a propensity score matched group of controls, and all patients were categorized according to ESC Guidelines.[4] As expected, within the CIT group, PE-related mortality was significantly increased in high-risk patients compared to non-high-risk patients (42% vs 12%, respectively). While CIT was significantly associated with increased 30-day mortality in the intermediate-risk group, statistical significance was not achieved in the high-risk group. There was no difference in mortality in high-risk patients with CIT according to applied therapy, nor was there difference in mortality based on CIT morphology. Thus, in high-risk patients, the presence of CIT appears less prognostically significant than

hemodynamic instability with regards to mortality. Two more recent studies involving patients with CIT and PE had similar findings: while CIT significantly predicted increased mortality in low- and intermediate-risk patients, it was not predictive for high-risk patients.[3,9]

Taken together, the above studies suggest that CIT is associated with a more severe clinical presentation and is clinically and prognostically significant in hemodynamically stable patients. However, it is not as prognostically significant in hemodynamically unstable patients. CIT may not add to the already substantial risk of mortality in this group. There is little evidence to suggest more aggressive or immediate treatment is associated with clinical benefit in the high-risk population, though it must be noted that these patients have exceedingly high mortality in the first 24 to 72 hours after presentation.[7,8] Barriers to interpretation of available evidence include exclusion of other higher-risk groups (e.g. cardiac arrest patients, post-surgical patients), exclusion of patients who did not receive an echocardiogram within a specified time frame, variable definitions of "massive" and "high-risk" PE, and the confounding impact of advanced treatment in the evaluation of prognostic significance. Further studies are needed to compare treatment efficacy in this group of patients.

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