A patient with pulmonary embolism takes a surprising HIT: a case report

Yishay Wasserstrum, Aaron Lubetzky, Orly Goitein, and Shlomo Matetzky

Background
Venous thromboembolism (VTE) is a common condition that may manifest as intermediate or high-risk pulmonary embolism (PE), requiring either primary or subsequent fibrinolytic therapy. In these cases, catheter-directed thrombolysis (CDT) has been shown to be beneficial.

Case summary
We present the case of a borderline obese but otherwise healthy 43-year-old male individual, who was admitted with acute intermediate- to high-risk PE requiring treatment with intravenous unfractionated heparin. After initial therapy failure, the patient received CDT, with subsequent clinical worsening, and a mixed result of imaging studies suggesting partial central worsening and partial peripheral improvement of the thrombotic burden and right ventricular (RV) function. After a multidisciplinary PE response team (PERT) consultation, the diagnosis of heparin-induced thrombocytopenia (HIT) with normal platelet levels was made. Therapy was changed to intravenous bivalirudin, with an excellent clinical response and complete recovery of RV function. The patient was discharged with oral rivaroxaban therapy, and on follow-up was otherwise well.

Discussion
Apparent failure of thrombolytic therapy for VTE warrants a clinical investigation into possible causes of a pro-thrombotic state. In this case, the diagnosis of HIT was surprising, especially due to only a mild decline in platelet levels that were well within normal range. We also acknowledge the significance of our PERT in the key diagnosis made in this case.

Keywords
Pulmonary embolism • Thrombosis • Thrombolysis failure • Catheter-guided thrombolysis • Heparin-induced thrombocytopenia • Case report

Learning points
• Patients suffering from venous thromboembolism and apparently fail to improve with thrombolytic therapy require a diagnostic workup for an ongoing prothrombotic stressor.
• Heparin-induced thrombocytopenia, which may be present even in patients with a mild decrease in platelet levels within normal range, should be considered in the differential diagnosis of patients with an ongoing prothrombotic state with no other apparent cause.
• The use of a pulmonary embolism response team (PERT) in the management of pulmonary embolism is supported by guidelines, and the multidisciplinary nature of this forum may assist in the management of challenging cases.

* Corresponding author. Tel: +972 54 4882737, Email: yishay.wasserstrum@sheba.gov.il
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Introduction

Venous thromboembolism (VTE) is a common, possibly life-threatening event that may occur idiopathically or in patients with clear thrombogenic stressors (i.e. thrombophilia, malignancy, trauma and immobilization etc.). Recommended treatment varies according to patient risk-stratification, and may span from initial oral anticoagulation for low-risk patients, to thrombolytic or surgical therapy in high-risk patients. Recently, catheter-directed thrombolysis (CDT) has been introduced as a possible alternative to the use of systemic thrombolysis. The rational is to provide a more locally targeted treatment, in order to allow the use of lower doses, and decrease the risk for adverse bleeding events. Catheter-directed thrombolysis has been described as an effective and safe option in several series and registries.

Although thrombolytic therapy has shown effectiveness in improving right ventricular (RV) function and haemodynamic stability, there remain gaps regarding the management of patients who fail to improve after an initial therapeutic course. In these cases, treatment options may include recurrent systemic thrombolysis, CDT, surgical thrombectomy, and consideration of extracorporeal membrane oxygenation. There is also a gap regarding recommendations on the workup for the potential causes of treatment failure.

Timeline

| Day 0: | Patient admission, began Unfractionated heparin |
| Day 5: | Hospital transfer |
| Day 6: | Catheter directed thrombolysis |
| Day 8: | Syncope |
| Day 9: | CT-Angiography showing worsening in central thrombus burden and improvement in peripheral lesions |
| Day 10: | Heparin-induced thrombocytopenia diagnosed, Unfractionated heparin stopped, began Bivalirudin |
| Day 16: | Clinical and echocardiographic improvement, Bivalirudin stopped, began oral Rivaroxaban |
| Day 18: | Hospital discharge |

Case presentation

A previously healthy 43-year-old male patient of Sephardic-Jewish descent presented to a local medical facility with chest pain and exertional dyspnoea that began earlier that day, following a week-long course that included loss of appetite and diarrhoea that resolved 1 day prior to presentation. He underwent a standard initial emergency department workup and was diagnosed with acute pulmonary embolism (PE), with a saddle-embolus and large bilateral thrombotic burden, RV systolic dysfunction, and mildly increased serum troponin levels. He was admitted to the local intensive cardiac care unit and therapeutic unfractionated heparin was started. Over the next few days, RV function further deteriorated despite therapy on serial echocardiographic studies, and the patient was transferred to our tertiary medical centre where several further treatment lines are available.

Upon arrival, the patient was asymptomatic and had stable vital signs. His routine laboratory panel showed normal renal function, high-sensitivity troponin-I, and lactate levels. His physical examination was positive for jugular venous distention but was otherwise non-remarkable. The patients’ electrocardiogram showed a normal sinus rhythm with a normal QRS axis and T-wave inversion in leads V1–4. The echocardiogram demonstrated a dilated RV with moderately reduced systolic function, and moderate estimated systolic pulmonary pressure (eSPAP) of 50 mmHg. The next day, CDT was performed using the EkoSonic Endovascular System, placed bilaterally. During 9.5 h, he received a total of 19 mg of alteplase. During therapy, D-dimer levels rose from a baseline level of 7000 ng/mL to a 121 000 ng/mL, while fibrinogen levels decreased from 560 mg/dL to 398 mg/dL. Unfortunately, a follow-up echocardiogram performed the next day did not show any significant changes.

At Day 2 after CDT, the patient suffered an episode of exertional syncope, with no associated arrhythmia, convulsions, or secondary trauma. At Day 3 after CDT, computed tomographic angiography showed a mixed picture composed of both worsening central thrombus burden, and partial improvement in some bilateral segmental and sub-segmental vessels. Compression Doppler sonography revealed a small right popliteal vein thrombus. Brain-natriuretic peptide (BNP) levels were elevated at 244 pg/mL, and troponin levels, that were previously normal, rose to a peak level of 88 ng/L. At this point in time, we knew that the patient was negative for anti-phospholipid antibodies, but further laboratory studies for hypercoagulability were still pending.
The case was presented at a multidisciplinary PE response team (PERT), and it was hypothesized that the patient, who at the time of clinical deterioration signified by the syncopal episode was treated with unfractionated heparin for a total of 10 days, might suffer from heparin-induced thrombocytopenia (HIT). A review of his previous platelet levels, which were mostly overlooked as they were well within normal range, showed a gradual downward trend, from initial levels at the range of 260 k/mcl to a nadir around the range of 180 k/mcl (Figure 3). This meant that the patient met the more minor platelet-level criteria for HIT of having a 30–50% decrease in platelet levels, as well as fulfilling the other three criteria of the 4 t’s score for HIT for a total of 6 points, which is classified as high probability (Table 1). The patient was tested for heparin immune antibodies, that were strongly positive at 6.8 U/mL, establishing the diagnosis of HIT. Other differential diagnoses were deemed as having a low probability due to a lack of supporting findings. These included, among others, disseminated intravascular coagulation, sepsis, microangiopathic haemolysis, systemic lupus erythematosus, antiphospholipid syndrome, and drug-induced thrombocytopenia.

The patient was switched from continuous intravenous heparin to bivalirudin therapy following the PERT meeting, and this was continued once the diagnosis of HIT was established. An echocardiogram performed the next day showed a normal sized and functioning RV, with moderately estimated eSPAP. Subsequent studies over the next few days also showed normal RV size and function, with a gradual decrease in eSPAP. Serum biomarkers such as troponin-I and BNP rapidly normalized, and platelet levels stabilized around 340 k/mcl. Previously drawn laboratory studies for hypercoagulability were positive for methylenetetrahydrofolate reductase heterozygosity, and antithrombin levels were low (58%), although this test was taken after several days of unfractionated heparin therapy.

The patient began mobilizing and was asymptomatic. After 6 days of bivalirudin treatment, doses ranging 0.4–2.0 mg/kg/h and titrating according to partial thromboplastin time, the patient was switched to oral rivaroxaban therapy. Initial rivaroxaban dose was 15 mg b.i.d., for 3 weeks, followed by a maintenance dose of 15 mg o.d. continued permanently during subsequent follow-up. The rest of the patients’ stay was unremarkable, and he was later discharged to his home in good clinical condition. At the 6-month follow-up visit, the patient was well and resumed his previous lifestyle without limitations. A small persistent asymptomatic thrombus was still present in his right popliteal vein. The complete clinical timeline is summarized in Figure 4.

Discussion

This case presents two unique challenges. The first is the management of a patient suffering from VTE with apparent failure to improve with anticoagulation and subsequent escalated therapy with CDT. In this case, the challenge was identifying this clinical sequela not as treatment failure, but a clinical response to an ongoing strong pro-thrombotic stressor concomitantly with anti-thrombotic therapy which overall had a weaker effect on net thrombogenicity. The second challenge is diagnostic, as the recognition of HIT in a patient who is not thrombocytopenic is not intuitive to most clinicians. In this case, the diagnosis was further advanced by convening our PERT to review and discuss this case. This emphasizes the importance of the multidisciplinary PERT as supported by current guidelines.1
Heparin-induced thrombocytopenia occurs in variable rates among different patient populations, depending on dosage, treatment duration and indication. In selected cases, incidence can be up to 0.5%. Thrombocytopenia as the most common clinical manifestation of HIT and is seen in 85–90% of cases. Approximately 5% of patients who do not have thrombocytopenia do show a decline in platelet levels of 30–50% from baseline.

As for the question of the management of patients who fail to respond to thrombolytic therapy, the authors believe that there is a great significance to further investigations regarding the possible causes of treatment failure, as it may open therapeutic options that are more appropriate and entail lower risk and a less invasive approach. We also hypothesize that this case may not represent failure of thrombolytic therapy or CDT per se, as there is ample evidence that the patient did respond to some extent—laboratory clotting markers, partial improvement on imaging—during the presence of a strong prothrombotic state.

Figure 2. Computed tomography angiography at baseline and after catheter-director thrombolysis. Axial image at the level of the Main pulmonary artery (MPA): A (Day 0): saddle embolus and bilateral filling defects in the Right pulmonary artery (RPA) and Left pulmonary artery (LPA). B (Day 9): saddle embolus and bilateral filling defects in the RPA and LPA, demonstrating worsening and increase in the thrombotic burden; axial image at the level of the Left lower lobe (LLL). C (Day 0): filling defects in the arteries supplying the LLL. D (Day 9): resolution of the filling defects in the arteries supplying the LLL; axial image at the level of the RPA. E (Day 0): filling defect in the RPA. F (Day 9): decrease in size of the filling defect in the RPA.
Table 1  Diagnostic criteria for HIT

| 2 points | 1 point | 0 point |
|----------|---------|---------|
| Thrombocytopenia | Platelet count fall >50% and platelet nadir ≥20 | Platelet count fall 30–50% or platelet nadir 10–19 | Platelet count fall <30% or platelet nadir <10 |
| Timing of platelet count fall | Clear onset between days 5–10 OR Platelet fall ≤1 day with prior heparin exposure <30 days | Consistent with days 5–10 fall, but not clear OR Onset after day 10 OR Fall ≤1 day with prior heparin exposure 30–100 days | Platelet count fall <4 days without recent exposure |
| Thrombosis or other sequelae | New thrombosis (confirmed) OR Skin necrosis OR Acute systemic reaction post-intra-venous unfractionated heparin bolus | Progressive or recurrent thrombosis OR Non-necrotizing (erythematous) skin lesions OR Suspected thrombosis (not proven) | None |
| Other causes for thrombocytopenia | None apparent | Possible | Definitive |

Adapted from Lo et al. This score is used to determine the likelihood of heparin-induced thrombocytopenia prior to confirmatory testing: 0–3 points—low probability (<1%); 4–5 points—intermediate probability (approximately 10%); and 6–8 points—high probability (approximately 50%).
Yishay Wasserstrum is a cardiology fellow in the Leviev Heart Center in the Sheba Medical Center in Tel-Ha’Shomer, Israel. After graduating from the Sackler School of Medicine in Tel-Aviv University in 2016, he went to complete an internal medicine residency program in the Sheba Medical Center in 2020. He has several publications in different respectable cardiology journals. He is a member of the Israeli Society of Cardiology and the European Society of Cardiology working group on myocardial and pericardial disease.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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