



## Case report

## A case of hemothorax secondary to intrapleural fibrinolytic therapy: Considerations for use of fibrinolytics in high-risk patients

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## ABSTRACT

Indwelling Pleural Catheters (IPC) are increasingly being used for management of recurrent pleural effusions (RPEs). Use of IPC for management of both malignant and non-malignant recurrent pleural effusions has been associated with complications such as dysfunctional or nonfunctioning IPCs. Alteplase, a tissue plasminogen activator (tPA) is often used to restore flow of non-draining IPC in symptomatic patients.

We present a case of a sixty-eight-year old patient with life-threatening pleural hemorrhage following intrapleural catheter instillation of tPA that was managed successfully by thoracotomy. Our case describe the importance of individualizing the fibrinolytic dose, frequency and the indwelling time in high risk patients. We have reviewed the current literature and recommendations for use of fibrinolytic therapy for IPC in high risk patients on anticoagulation.

### 1. Introduction

With frequent use of Indwelling Pleural Catheters (IPCs) for the management of recurrent pleural effusions (RPEs), there has been an increased incidence of dysfunctional and non-draining IPCs encountered in clinical practice. The underlying mechanism is believed to be fibrin mediated disruption of pleural fluid drainage. While partial blockage can be managed initially by flushing the catheter with saline solution, certain cases may require either invasive or noninvasive strategies [1,2]. Alteplase, a tissue plasminogen activator (tPA) is often used to restore the flow of non-draining IPC in symptomatic patients [3]. However, there are no specific guidelines addressing the safety, ideal dosing, pharmacokinetics, and efficacy of tPA in patients on concurrent anticoagulation. The ideal dosing, frequency, diluent, and the dwell time for intra-pleural catheter administration of tPA is largely derived from anecdotal evidence and vary amongst institutions given the scarcity of available literature. Hemothorax is a rare but potentially life-threatening complication associated with the use of tPA in the IPCs. Herein we report a case of a sixty eight-year-old patient on anticoagulation therapy with apixaban who suffered a life threatening

pleural hemorrhage following the instillation of tPA in the IPC requiring emergent thoracotomy.

### 2. Case presentation

A 68-year-old patient with a history of atrial fibrillation on apixaban and chronic-kidney disease-stage-4 presented to the emergency department (ED) with shortness of breath of 1-week duration. After-maximally optimizing the renal and cardiac therapy, a right-sided IPC was placed for the palliation of RPE secondary to heart failure with reduced ejection fraction, three months prior to presentation.

Computed tomography (CT) of the chest in the ED revealed moderate pericardial effusion and bilateral pleural effusions with a stable right IPC (Fig. 1).

Bedside echocardiography revealed pericardial effusion with associated tamponade for which an emergent pericardiocentesis was performed with the evacuation of 300 ml of pericardial fluid followed by insertion of a pericardial drain. The hospital course was complicated by worsening kidney function requiring hemodialysis. Apixaban was discontinued on admission and the patient was transitioned to intravenous

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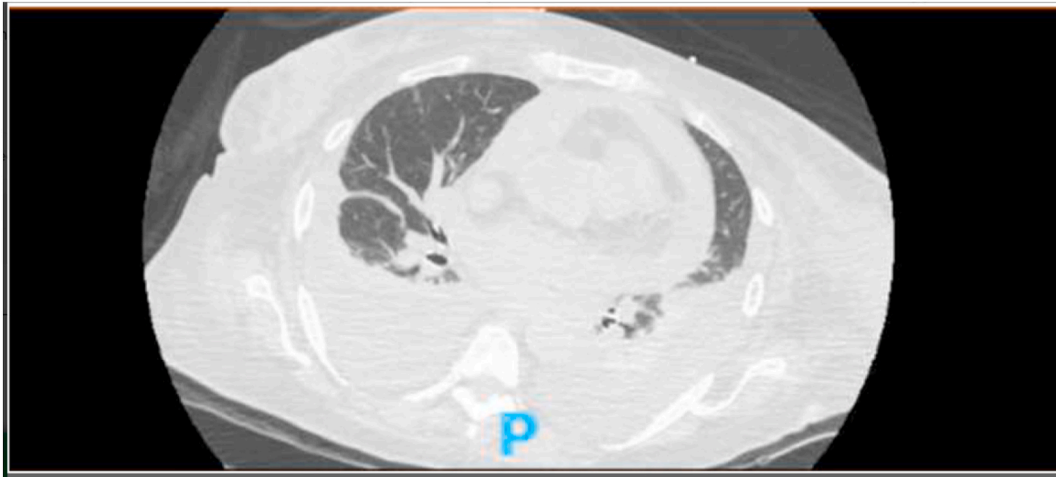


Fig. 1. Non contrast axial chest-computed tomography lung window depicting Bilateral Pleural Effusion.

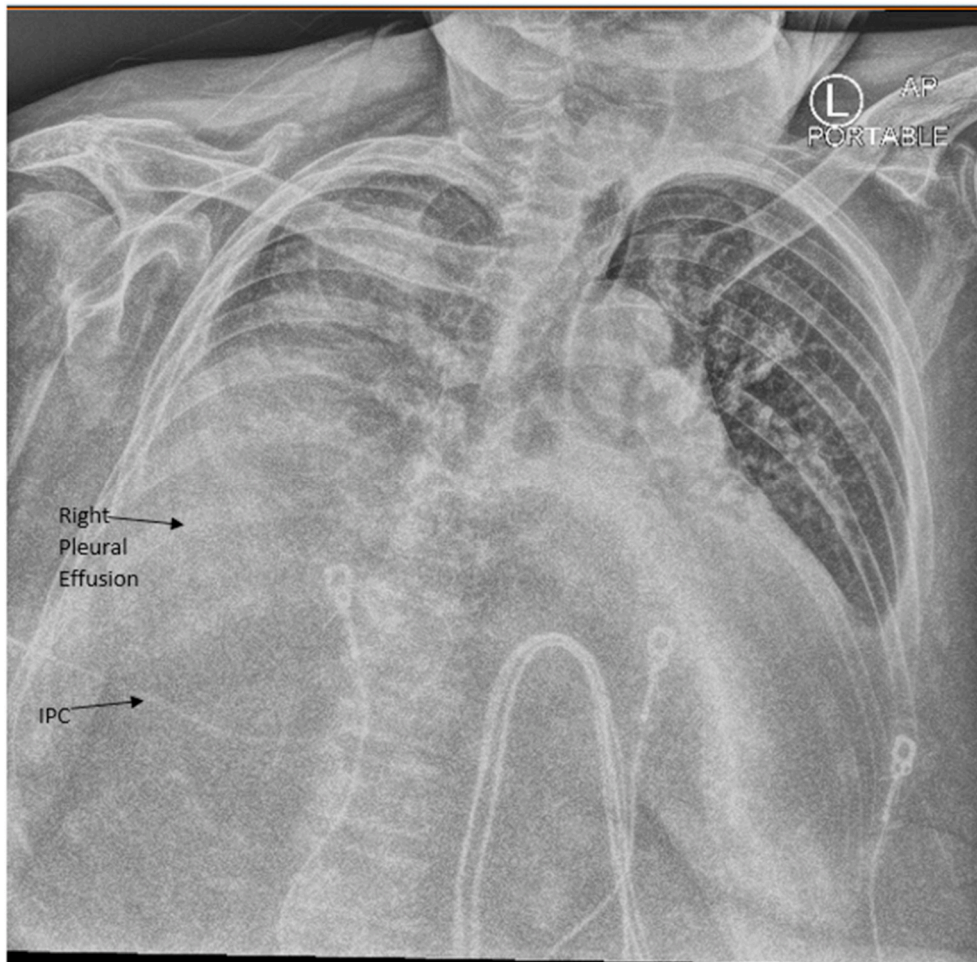


Fig. 2. Chest X-Ray AnteroPosterior view revealing bilateral pleural effusions, Right > Left. Right Sided Indwelling Pleural Catheter (IPC).

heparin. On day seven, chest Xray (CXR) revealed significant right pleural effusion raising suspicion for nonfunctional IPC. IPC flushing with saline was attempted but was unsuccessful. After discussion of benefits and risks of IPC instillation of tPA with the patient, a single dose of 4 mg tPA diluted in 20 ml normal saline was instilled through the IPC and allowed to dwell for 1 h. The patient tolerated the procedure well with drainage of greater than 150 mL(ml) of pleural fluid. The patency

of the IPC was deemed to be restored. The patient had a prolonged hospital course during which apixaban was subsequently resumed on the 10th day of hospitalization. Subsequently, with decreasing IPC drainage and worsening right pleural effusion confirmed by the CXR, flushing of the IPC with saline was attempted on day 17th. As it was unsuccessful, a total of 4 mg of tPA diluted in 20 ml saline was instilled through the IPC with a dwell time of 4 hours. The patient subsequently

**Table 1**  
Highlighting the studies reporting hemothorax following use of intrapleural thrombolytics.

| STUDY                       | Sample Size | Effusion type  | Intrapleural thrombolytic therapy use | Anticoagulation or antiplatelet use   |
|-----------------------------|-------------|--|---------------------------------------|---|
| Maskell et al., 2005 [11]   | 427 adults  | Empyema; Parapneumonic complicated effusion  | Placebo or streptokinase              | Unspecified   |
| Ruiz et al., 2006 [12]      | 1 adult     | Empyema  | Alteplase                             | Nil   |
| Gervais et al., 2008 [13]   | 66 adults   | Empyema (27 patients), parapneumonic complicated effusion (26 patients), hemothorax (8 patients), postoperative effusion (4 patients), and malignant effusion (1 patient). | Alteplase                             | 1 patient warfarin, 2 Patient Low molecular weight heparin and 1 Patient unfractionated heparin |
| Goralski et al., 2009 [14]  | 1 adults    | Benign Effusion  | Alteplase                             | nil   |
| Chai and Kuan 2011 [15]     | 1 adult     | Parapneumonic complicated effusion   | Streptokinase                         | Nil   |
| Anevlavis et al., 2011 [16] | 2 adults    | Parapneumonic complicated effusion   | Alteplase                             | Prophylactic dose of subcutaneous low-molecular weight heparin (tinzaparin 3,500 IU)            |

reported worsening shortness of breath associated with right-sided chest pain. The coagulation profile showed INR of 1.40 and PTT of 32.90s. The CXR demonstrated large right pleural effusion (Fig. 2).

The IPC was drained with the evacuation of 1500ml bloody pleural fluid. With a pleural fluid/serum hematocrit ratio of 0.6, the pleural fluid was suggestive of a hemothorax. Blood transfusion protocol was activated during which patient received six units of packed red blood cells, 1500 units of K-centra, 10 units of cryoprecipitate, 10 mcg of desmopressin (DDAVP) and three units of fresh frozen plasma. The patient subsequently underwent emergent exploratory thoracotomy with removal of right chest blood clots followed by the insertion of two right-sided large-bore chest tubes. The patient had a prolonged hospital course complicated by bacteremia and decompensated heart failure.

### 3. Discussion

IPCs are silicon tubes with a one-way valve, which are tunneled and secured subcutaneously. After minimal training, the patients or the caregivers can perform ambulatory pleural effusion drainage. The PleurX catheter (CareFusion, Vernon Hills, IL, USA) approved by the US Food and Drug Administration (FDA) in 1997 for management of malignant pleural Effusion and further licensed in 2011 for nonmalignant pleural effusion, is being frequently used for the outpatient management of RPEs [4,5]. The average time for pleurodesis is reported to be 95 days, although the rate of pleurodesis can be variable [6]. Recent studies have evaluated the effectiveness of IPC instillation of tPA in restoring the flow of non draining IPC when the saline flush fails. Being a non-invasive modality, it is considered an ideal strategy to restore the flow. The tPA converts plasminogen to active protease plasmin which further

degrades fibrin into soluble products [2,7,8]. The degree of systemic absorption of intrapleural administered tPA is highly variable and remains unknown. The pharmacokinetics and potential activity of tPA varies among individuals depending upon pleural fluid characteristics (pH, protein), comorbidities (end-stage renal disease, sepsis, coagulopathy) and possibly with concurrent use of anticoagulation [7]. The algorithm used at our institution is similar to the one described by Vial et al. [9].

The IPC is first flushed with 20–30 mL of sterile saline with an outcome termed successful if pleural drainage is > 150 mL. For saline-flush failure cases, 4 mg tPA diluted in 20 cc saline, is instilled in the IPC with 1 hour dwell time. If > 150 mL fluid is drained, tPA treatment is considered successful. Drainage of <150 mL fluid is followed by a second dose of 4 mg tPA with prolonged dwell time (12–24 hours).

To the best of our knowledge, there are no phase 1 dose-escalation studies or head-to-head comparisons to establish the optimal dosage of tPA for restoring the patency of IPCs. large heterogeneity is noted in the clinical practice regarding the ideal dosage of tPA (2–20 mg)2, [7–9]. Hart et al. [10] demonstrated the success of 1mg tPA with 5mg DNase given twice daily for 2.5 days (total 5 doses) while Lan et al. published the efficacy of a single dose of 0.5 mg tPA for restoring patency of IPC [2]. The concurrent effect of Direct Oral Anticoagulants (DOACs) on bleeding in patients receiving Intrapleural tPA is uncertain. Although the use of tPA for clogged IPCs is considered a non-invasive strategy, cases of life-threatening pleural hemorrhage have been reported in the literature (Table 1).

To the best of our knowledge, our case is probably the first one to report the complication of hemothorax with intra-pleural catheter tPA use in a patient on apixaban. DOACs have gained significant popularity for the treatment of a variety of conditions including but not limited to atrial fibrillation, venous thromboembolism, ischemic stroke [17]. Clinicians should be cautious using intra-pleural catheter tPA in such high-risk patients.

### 4. Conclusion

This case report adds to the limited literature on complications of pleural hemorrhage following IPC tPA therapy in patients on direct oral anticoagulants. We propose using the lowest possible dose of tPA in high-risk patients to prevent this life threatening complication. Further studies are required to determine the optimal dose, safety, and effectiveness of IPC tPA in patients on concurrent anticoagulants.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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