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Very low-dose intrapleural tPA for indwelling pleural catheter-associated symptomatic fluid loculation

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Abstract

Indwelling pleural catheters (IPCs) are effective management options for malignant pleural effusion. Symptomatic fluid loculation is a recognized complication of IPC use and is usually managed with intrapleural instillation of fibrinolytic drugs, such as tissue plasminogen activator (tPA). A previous multicentre observational study showed significant heterogeneity among centres in their dosing regimen for tPA (from 2 to 20 mg) in treating symptomatic loculations. Potential pleural bleeding, especially in high-risk patients, often deters clinicians from initiating intrapleural fibrinolytic therapy. Lower doses of tPA may reduce bleeding risks. This case report describes the successful use of 0.5 mg (the lowest reported dose) of tPA in a patient with significant bleeding risks whose IPC was complicated by symptomatic loculation.

Introduction

Malignant pleural effusion (MPE) often requires repeated drainage to provide symptomatic relief [1]. Treatment of MPE with an indwelling pleural catheter (IPC) allows for ambulatory fluid drainage, reduces time spent in hospital, and may promote spontaneous pleurodesis [1,2].

Symptomatic loculations can complicate IPC use in up to 14% of IPC-treated patients [3]. The minimally invasive management of symptomatic loculations involves the administration of intrapleural fibrinolytic therapy, such as tissue plasminogen activator (tPA), to lyse adhesions [1,3]. However, this carries the risk of pleural bleeding [1]. Prior studies showed significant heterogeneity in the dose of tPA administered (2–20 mg) among centres as the optimal dose of intrapleural fibrinolytic therapy has not been established [1]. There is an ongoing search for the lowest effective dose of tPA that minimizes the risk of complications while maintaining efficacy.

This case report describes the successful use of the lowest reported dose of tPA in a patient with a high risk of bleeding whose IPC was complicated by symptomatic loculation.

Case Report

A 74-year-old female had known stage IV high-grade follicular lymphoma (blastoid variant), diagnosed 2 years prior to this presentation. Her disease had progressed despite exhausting several lines of chemotherapy. At the time of this presentation, her management was palliative in intent and included oral prednisolone and regular blood transfusions for persistent pancytopenia (due to bone marrow failure). Her other medical history included breast cancer treated with lumpectomy, radiotherapy, and tamoxifen; suppressed hepatitis B on lamivudine; glaucoma; and cold agglutinins.

About 1 year prior to this presentation, she developed bilateral, but left-predominant, biochemically confirmed chylothoraces. Her left chylothorax continued to recur despite diet modifications, prior therapeutic thoracentesis, and subsequent talc slurry pleurodesis. Her pancytopenia posed a high risk for repeated pleural drainages. An IPC was therefore inserted for ambulatory drainage, which was performed twice or thrice a week (removing ~300 mL each time) with good symptomatic response.

Two months after her IPC insertion, she presented to the clinic as no fluid could be drained from the IPC. She reported worsening dyspnoea and lethargy. Blood tests demonstrated known pancytopenia, including severe thrombocytopenia of 13×10^9/L, anaemia (haemoglobin 70 g/L), and leukocytopenia (2.49×10^9/L). Her procalcitonin level was normal (0.08 μg/L), and C-reactive protein (CRP) was mildly raised (44 mg/L). Cultures of blood and pleural fluid did not yield any organisms.

Chest X-ray demonstrated a large locule of pleural fluid (Fig. 1A), confirmed on ultrasound (Fig. 2A,B). No pleural fluid could be aspirated via the IPC, which flushed well with saline, indicating tube patency. A diagnosis of symptomatic pleural fluid loculation was made. The benefits and risks of intrapleural fibrinolytic therapy were discussed.

Given her high bleeding risk from severe pancytopenia, a decision was made to attempt a very low starting dose of 0.5 mg tPA after transfusions of 1 unit of platelets and 1 unit of packed red blood cells (which raised her haemoglobin and platelet counts to 85 g/L and 55×10^9/L, respectively).

A single dose of 0.5 mg tPA, diluted up to 50 mL with normal saline, was instilled through the IPC and was allowed to dwell for 45 min. The IPC subsequently drained 900 mL of blood-stained chylous fluid (Fig. 1C) over 12 h, with good symptom relief. Her haemoglobin remained stable with no clinical evidence of iatrogenic haemothorax or systemic bleeding. Chest X-ray (Fig. 1B) and pleural ultrasonography demonstrated complete resolution of the loculated effusion (Fig. 2C,D). She was discharged home within 24 h. Her IPC continued to drain well at her 2-month follow up after admission, with no recurrence of loculations on imaging.

Discussion

This is the first report of the successful and safe use of a very low-dose tPA intrapleurally for the treatment of IPC-related symptomatic loculation. IPC use is increasingly being adopted worldwide. Symptomatic loculated effusions are known to complicate up to 14% of patients following IPC insertion [3]. Restoring the drainage function of the IPC is the ideal outcome as alternative strategies, for example, recurrent pleural aspiration, inserting a supplementary catheter, or surgery, offer only a temporary solution and are invasive.

A multicentre observational study of intrapleural fibrinolytic therapy for IPC symptomatic loculation demonstrated significant clinical response, improvement in pleural fluid drainage, and reduction in the radiological appearance of pleural fluid in the majority of patients [1]. Systemic bleeding did not occur, but pleural bleeding, although rare, was reported in a small number (2 of 66) of patients [1].

There are no phase I dose escalation studies or head-to-head comparisons of different fibrinolytics to establish the most effective drug and dosage for intrapleural therapy of loculated effusions. Heterogeneity is therefore common in clinical practice. Interestingly, there is increasing evidence to support the use of lower doses of tPA (with deoxyribonuclease (DNase)) as intrapleural therapy for pleural infections [4]. A prior case report has described the successful use of tPA doses as low as 1 mg, together with 5 mg DNase, in the setting of pleural infection in a patient with high bleeding risks [5].

It is likely that the minimal effective dose of intrapleural fibrinolytic therapy may vary among patients. Until there is a reliable predictive system, starting with a very low dose is an attractive option, especially in patients at high risk of

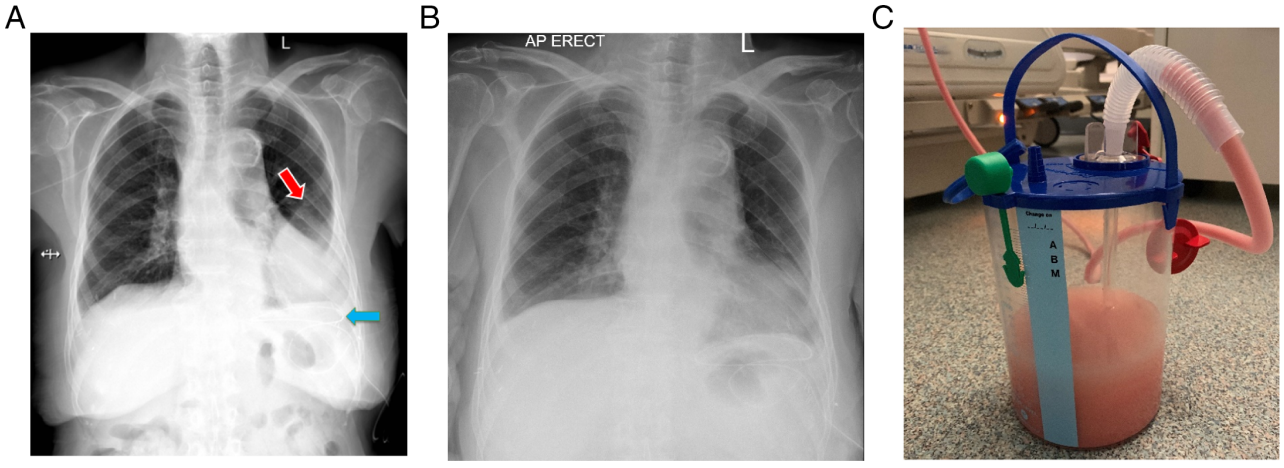

Figure 1. Chest X-ray images (A) before and (B) after administration of low-dose tissue plasminogen activator (tPA). The red arrow shows the edge of the locule, and the blue arrow shows indwelling pleural catheter. (C) Blood-stained chylous fluid drained after tPA administration.

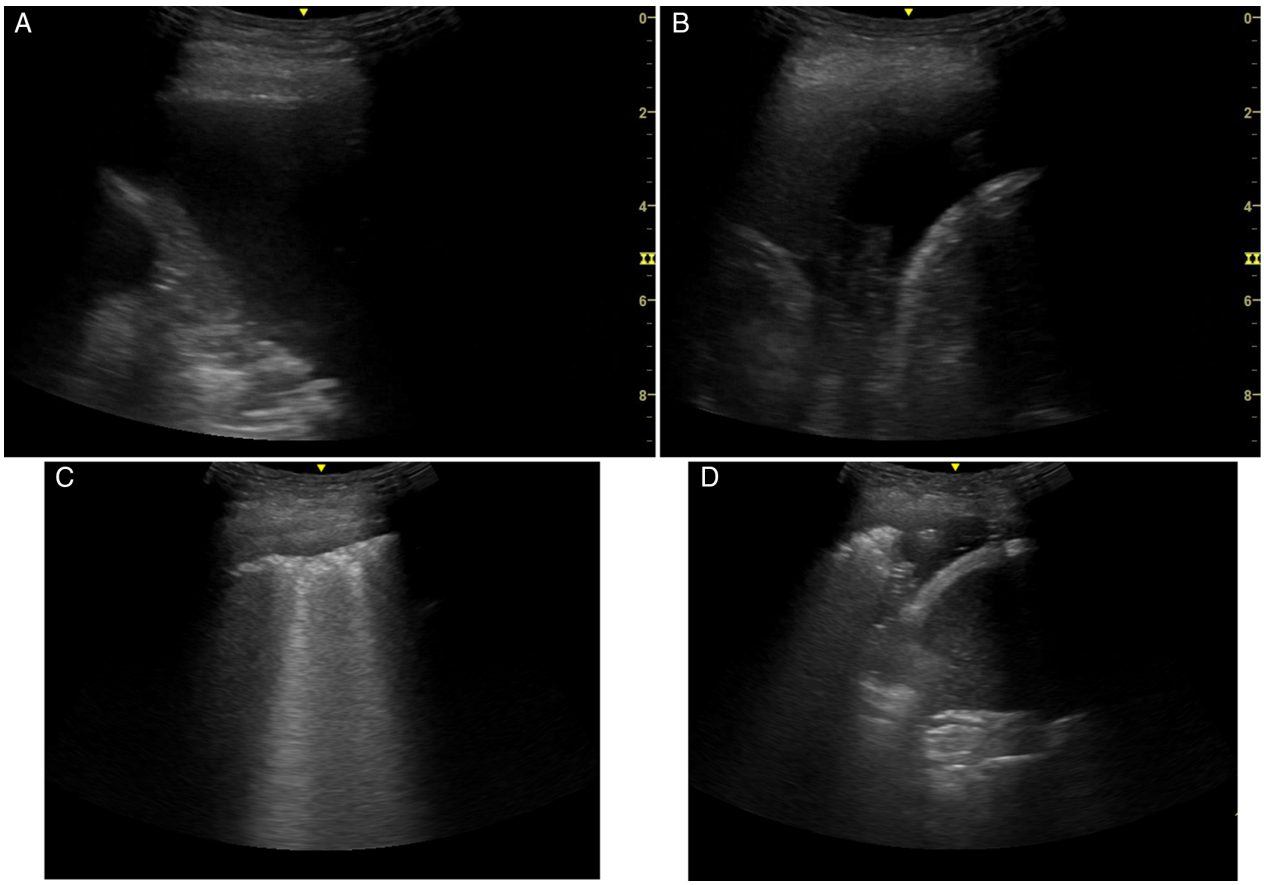

Figure 2. Pleural ultrasound images of an anechoic pleural effusion at mid thoracic level (A) and in the costophrenic angle (B) before use of a low-dose intrapleural tissue plasminogen activator. Ultrasound images in same locations showing lung expansion post-drainage of effusion with visible visceral pleura (C) and trivial residual effusion at the costophrenic angle (D).

bleeding. Dose escalation can always be performed if there is no timely clinical response.

To the best of our knowledge, this is the lowest reported dose of tPA used to treat symptomatic loculated pleural effusions. This suggests that lower doses may be used successfully, with implications for a reduced side effect profile and costs, and therefore warrants further exploration.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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