CASE REPORT

Low-dose intrapleural alteplase (without deoxyribonuclease) in complicated parapneumonic effusion: case series and literature reviews

Carol Lai,¹ Nurashikin Mohammad,² Tidi Maharani Hassan,¹
Mohamed Faisal Abdul Hamid^{1,3}

¹Department of Medical,
Pusat Perubatan Universiti
Kebangsaan Malaysia, Cheras,
Kuala Lumpur, Malaysia

²Department of Internal
Medicine, Universiti Sains
Malaysia, Kota Bharu, Kelantan,
Malaysia

³Department of Medical,
Pusat Perubatan Universiti
Kebangsaan Malaysia, Cheras,
Kuala Lumpur, Malaysia

Correspondence to
Nurashikin Mohammad,
elshikina@gmail.com

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SUMMARY

This case series reviews two cases of elderly patients who presented with fever, cough and shortness of breath. Clinical examinations and initial chest radiographs confirmed unilateral pleural effusion. Thoracenteses were consistent with exudative pleural effusion. We commenced intravenous antibiotics treating for parapneumonic effusions. The first case showed persistent effusion despite drainage, and the second case had a little aspirate from pleural tapping. Subsequent ultrasound of the thorax showed multiloculated effusions. We made the decisions for intrapleural fibrinolytic therapy using low-dose alteplase 2.5 mg each time, in view of the elderly patient as sacrosanct for risk of bleeding. Furthermore, DNase was not used, as it is not yet available in our setting. Both of our patients had good clinical and radiological outcomes, without the need for surgical interventions.

BACKGROUND

Pleural infection is increasing worldwide; in the USA alone, it is responsible for 90 000 hospital admissions a year and has proven to be a global health burden.¹ Mortality in adult patients approaches 20%, and up to 50% require surgical intervention.¹ Parapneumonic effusions make up about 40% of all bacterial pneumonia. Drainage of infected fluid is key to successful management; however, often times the effusion is loculated, and drainage of the pleural effusion in addition to administration of intravenous antibiotic appears to be ineffective. Difficulty in drainage of infected pleural fluid is due to presence of fibrous septations and high fluid viscosity.²

Intrapleural fibrinolytic therapy was first used in the 1970s and has been proven successful in numerous trials.^{3–4} Antifibrinolytic agents that were used are streptokinase, urokinase and recombinant tissue plasminogen activator (rtPA). However, the success rates, study design and dosage of antifibrinolytic agents vary in different reports. Due to cost, accessibility and safety, the feasibility of IPFT in complicated pleural effusion will also depend on the dosage of these agents. In our centre, we have recently started to incorporate this strategy using low-dose rtPA-alteplase. We report on two cases of loculated pleural

effusion treated with low-dose intrapleural 2.5 mg alteplase without DNase with positive outcomes.

CASE PRESENTATION

Case 1

A previously healthy 75-year-old woman was admitted for a 2-week history of breathlessness with worsening symptoms over the past 3 days. There was no history of fever or cough, but she had loss of appetite and loss of weight. She has had chronic lower back pain due to spondylolisthesis. On examination, she had reduced breath sounds and stony dullness over the right lung. She was febrile but otherwise had stable vital sign with oxygen saturation of 96% on 3 L of oxygen. There were no palpable lymph nodes or clubbing.

Case 2

An 82-year-old woman with type 2 diabetes mellitus, hypertension and dyslipidaemia presented with a 2-week history of cough associated with breathlessness. The cough was worsening over 1 week together with high-grade fever. Clinically she was tachypneic with respiratory rate of 40 breaths per minute; heart rate was 100 beats per minute and she was febrile at 38°C, with normal blood pressure. Her arterial blood gas showed type I respiratory failure and she required high-flow mask oxygen.

INVESTIGATIONS

Case 1

Initial chest radiograph showed a right pleural effusion, which constituted more than 50% of the hemithorax (figure 1A). Septic parameters were raised with a total white count (TWCC) of 18.7×10^9 , C reactive protein (CRP) of 9.64 mg/L and erythrocyte sedimentation rate of 75 mm/hour. Pleural fluid showed sterile, exudative features with pleural lactate dehydrogenase (LDH) of 425 IU/L. There was no pleural pH or cell differential counts available. The ratio of pleural and serum LDH and protein was 1.8 and 0.9, respectively.

CT thorax (figure 2A–C) was performed, which showed a constellation of non-enhancing collapsed consolidation of the right lower lobe and right loculated pleural effusion. In addition, there was presence of interlobular septal thickening in the right

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Figure 1 Chest X-ray (CXR) of case 1 demonstrating right pleural effusion occupying more than 50% of the right hemithorax (A). CXR postpigtail catheter insertion revealing persistent right pleural effusion (B). Minimal pleural effusion was observed after three doses of alteplase 2.5 mg (C).

middle and right lower lobes and the inferior lingula segment of the upper lobe.

Case 2

The infective blood parameters were raised: TWCC 14×10^9 ; CRP 25 mg/L, with evidence of acute kidney injury; and creatinine of 151 $\mu\text{mol/L}$. A bedside ultrasound showed multiple locules at the mid and upper zones, with a diameter of 3 cm each (figure 3A). Chest radiograph (figure 4A) revealed left-sided effusion involving 25% of the hemithorax. Pleural fluid analysis revealed exudative effusion with pleural LDH of 1150 IU/L (ratio of pleural to serum 2.1); however, no pleural pH or cell differential counts were available. The gram stain for pleural fluid was negative and the pleural:serum protein ratio was 0.8.

The pigtail was removed and a Rocket 12F intercostal chest drain (ICC) was inserted in the left middle posterior locule, which drained 80 cc serous fluid. Repeated chest radiograph (figure 4B) and bedside ultrasound revealed only slightly smaller dimension locules; hence, she was considered for IPFT.

DIFFERENTIAL DIAGNOSIS

Both of our patients had complex pleural effusion (parapneumonic) in view of the presence of multiple loculations and

septations. There was no evidence to suggest empyema (ie, no frank pus, although pleural pH was not tested).

For complex exudative pleural effusions:

- ▶ Bacterial empyema
- ▶ Pleural tuberculosis (this differential must be considered at all times, in view of high tuberculosis prevalence in Malaysia)
- ▶ Malignant effusion
- ▶ Malignant mesothelioma
- ▶ Fungal infection.

TREATMENT

Case 1

We performed right-sided thoracentesis in addition to the broad-spectrum intravenous antibiotics coverage. Intravenous ceftriaxone 2g daily was given. Thoracentesis was performed three times, drained 1.5 L, 700 cc and 1.4 L haemoserous fluid, respectively. However, serial chest radiographs showed persistent right-sided pleural effusion. Ultrasound of the thorax revealed multiloculated pleural effusion. 8F pigtail was inserted on day 6 of admission and 345 cc serous fluid was drained over 2 days (figure 1B). The biggest and most accessible locule was targeted. Subsequently, there was a minimal drainage observed.

Figure 2 CT thorax of case 1 revealed constellation of non-enhancing collapsed consolidation of right lower lobe and right pleural effusion (A–C).

Figure 3 Thoracic ultrasound illustrating multiloculated effusion before the instillation of tissue plasminogen activator (A). Thoracic ultrasound after three doses of tPA demonstrating minimal residual effusion (B).

The drainage was still minimal despite intermittent catheter flushing with saline. A repeated bedside ultrasound thorax revealed two locules. One was from anterior examination of the chest and the other was on posterior examination.

A decision for rtPA-alteplase was made on day 8 of admission. The constituent of 2.5 mg alteplase in 50 mL 0.9% sodium chloride (NaCl) was instilled through the chest drain. A low dose of alteplase was considered in view of the patient being petite and an elderly person. Therefore, it is sacrosanct to reduce the risks of intrapleural bleeding. The pleural drain was clamped for 45 min before allowing free drainage.

Case 2

Broad-spectrum intravenous antibiotic was commenced. Intravenous ceftriaxone 2 g daily was given, but it was changed to intravenous piperacillin/tazobactam (4.5 g three times a day) as the patient still had fever after 48 hours. A blind pleural aspiration was attempted, but only 80 cc serous fluid was drawn. She was noted to have loculated pleural effusion on ultrasound. The following day (on day 4 of admission), she was sent for a chest drain insertion under interventional radiologist using 12Fr ICC drainage targeting the biggest locule. A total of 300 mL of haemorrhagic fluid was drained over 3 days.

Three doses of alteplase of 2.5 mg in 50 mL of 0.9% NaCl were given via the ICC. Then, 180 cc and 150 cc of haemorrhagic fluid were drained after the first and third dose of alteplase, respectively.

OUTCOME AND FOLLOW-UP

Case 1

On the next day, 800 cc pleural fluid was drained. A second and a third administration of alteplase were given the following day, 8 hours apart between each dose. Another 760 cc pleural fluid was drained. The patient's general condition and cough improved and she remained afebrile. The chest radiograph showed improvement (figure 1C), and she was discharged without immediate complications.

Case 2

Our patient improved and there were resolutions of both fever and breathlessness. Her oxygen saturation improved under room air. The infective blood parameters and kidney functions normalised (CRP 8.53, 6.62 and 2.08 mg/dL after three doses of tissue plasminogen activator (tPA), respectively). Thoracic ultrasound after three doses of tPA demonstrated minimal residual effusion (figure 3B).

Chest radiograph prior to discharge showed improvement in the pleural effusion (figure 4C). She was discharged with oral antibiotics (amoxicillin/clavulanic acid 625 mg tablet twice a day). On follow-up 6 weeks later, she remained well and asymptomatic with total resolution of the effusion.

DISCUSSION

Understanding the pathophysiology of complicated pleural effusions may aid in comprehending the use of IPFT for pleural management. In complicated parapneumonic effusion, white blood cells migrate to the pleural space as a permeable factor and release fibrinogen. The fibrinogen will then convert into fibrin, which causes the tissue surfaces to adhere and trap causative pathogens.³ This entrapment causes a hindrance to host defence mechanism and antibiotics from reaching the site of infection.⁵ Low fibrinolytic activity and elevated concentrations of plasminogen activator inhibitors (PAI) have been observed in pleural infection.⁵

IPFT is more effective if administered in the early fibrinopurulent stage of parapneumonic pleural effusion.⁶ It was first described in the late 1940s. Streptokinase, urokinase and alteplase have been used for these conditions. Streptokinase and urokinase are thought to be equally as effective, although there is no head-to-head trial comparing the two drugs. However, urokinase is the generally preferred agent as streptokinase may lead to sensitisation and potentially lead to the development of antibodies towards the drug,

Figure 4 Chest X-ray (CXR) of case 2 shows left-sided pleural effusion involving 25% of the hemithorax (left). CXR after pigtail catheter insertion revealed persistent left-sided effusion (centre). CXR after the instillation of the first dose of tissue plasminogen activator demonstrating reduction in the size of the effusion (right).

which may reduce its therapeutic efficacy.^{1 6} Based on systemic review by Cameron and Davies,⁷ in the earlier studies included in their review, IPFT confers significant benefit in reducing the requirement for surgical intervention but not in newer studies. The reason for this discordance is uncertain.

Intrapleural recombinant tissue or alteplase has been suggested to be more effective than streptokinase.⁶ A unique characteristic of tPA is that it is fibrin-selective and preferentially activates plasminogen at the surface of a clot. Active protease plasmin degrades fibrin into soluble products.¹ During pleural infection, cytokines (including tumour necrosis factor- α , interleukin-8 and transforming growth factor- β) are elevated within the pleural space. They are capable of stimulating PAI-1 release from mesothelial cells.¹ Fibrin deposition and loculation within the infected pleural space are inevitable due to the imbalance between activators and inhibitors of the fibrinolytic system creates a profibrotic stage.¹

Abu-Daff *et al* presented 227 patients with complicated pleural effusions who received IPFT and did not resolve with simple drainage and antibiotic therapy. They reported an 80% overall success rate, with an 85% success rate in patients with infections. However, the success rate was lower for loculated malignant effusions (59%). Pleural thickening was the single most important predictor (thickening >2 mm in CT scan) for failure.³ In another study, Thommi *et al*⁴ treated 120 patients (93 pleural infections; 10 haemothorax; 17 malignant) with an overall success rate of 85% with complete resolution, 8% unspecified partial resolution and 7% failed therapy.

IPFT has been proven to be effective but not without adverse effects. Chest pain is the most common side effect due to increment of fluids and breakage of adhesions that could irritate the innervated parietal pleural.¹ This is why adequate analgesics are required prior to the first dose of IPFT. Other adverse effects include circulating plasminogen resulting in systemic lytic state and bleeding risks.¹ Reports for tPA given intravenously are known to cause severe bleeding in 1.8% and moderate bleeding risk of 11.8%.¹ The degree of systemic absorption of tPA from the pleural space is unknown, but postulated to be low. However local bleeding within the pleural cavity has been reported.¹ tPA has a high molecular weight (>65 000), and therefore it is postulated that it does not cross the pleural membrane through passive diffusion but is most likely cleared via lymphatic drainage.¹ Sixty minutes following IPFT, the chest drain was allowed for free drainage, and any drug that has not been cleared from the pleural space should be removed before the next instillation of tPA.¹ This would explain low incidences of IPFT-induced bleeding in clinical studies.

To date, high risk of bleeding or bronchopleural fistula is the most common contraindication of IPFT in patients; however, other contraindications of intrapleural tPA/DNase are not well defined.¹ tPA has been shown to be safe even when used sequentially. Popowicz *et al*⁸ described two courses of intrapleural tPA with DNase administered for two different loculated pleural effusions with good clinical outcome and no adverse effects. The same author illustrated a patient who was unintentionally administered up to six instillations of tPA (10 mg) and DNase (5 mg) intramuscularly via a malpositioned chest drain.⁹ The patient was reported to have experienced minimal discomfort but no signs of tissue inflammation or necrosis on CT thorax.

Cell degradation product leads to increase in viscosity of pleural fluid, which makes it more difficult to drain. Although the use of IPFT alone is promising, introducing DNase content reduces the pus viscosity of the pleural fluid. Light *et al*¹⁰ showed that streptokinase in combination with DNase was more effective in reducing

pus viscosity compared with using antifibrinolytic (streptokinase, urokinase) or saline alone.

Rahman *et al* conducted a landmark study (Multicenter Intrapleural Sepsis Trial (MIST) 2). Two hundred and ten participants were enrolled and randomly assigned into three arms. They received either 10 mg tPA or 5 mg of DNase alone, combination of tPA and DNase, or placebo. The trial showed that treatment with combination tPA and DNase improved drainage of infected fluid. However, use of each active agent alone was ineffective. This trial supports MIST 1 trial and suggests a new therapeutic strategy for this disease. tPA and the additional cleavage of uncoiled DNA by DNase increase the efficacy of fibrinolytic therapy. Based on the MIST 2 trial, only 6% of patients had serious event (two patients had intrapleural bleed, one had haemoptysis in the tPA-DNase group).¹¹

Although IPFT has been around for decades, the use of low-dose, that is, 2.5 mg, intrapleural alteplase is not established and less adopted in many institutions including Malaysia. A study performed by Popowicz *et al*¹² using 5 mg of tPA (with DNase) appeared comparable to 10 mg tPA. Due to safety reasons, the use of low-dose alteplase is intuitively desired to avoid bleeding risk. We used a total of 7.5 mg as compared with the standard regimen of 30 mg. We were cautious mainly because both of our patients were in extreme age. While systemic absorption of intrapleural alteplase has not been directly studied, there were reported cases of bleeding, including massive haemothorax using standard regimen of intrapleural fibrinolytic tPA and streptokinase. The purpose of this article is to highlight the successful outcomes using lower dose compared with standard regimen, as well as the tPA without DNase in pleural infections. Furthermore, non-inferior studies are required to examine the efficacy compared with higher dose of alteplase, which has been shown to be effective in our case series.

We report two successful cases of loculated pleural effusion using low-dose alteplase without DNase. An ideal standard of care was also complied by using ultrasonography to assess diagnosis and effects of each intervention. Intrapleural tPA may reduce hospital stay and obviate invasive surgical intervention. To our knowledge,

Learning points

- Ultrasound of the thorax is important based on grade A evidence for assessment of complex pleural effusion and should be considered as a point-of-care testing. Furthermore, a blind aspiration is not advisable like in case 2.
- Low-dose intrapleural tissue plasminogen activator (tPA) should be considered in elderly patients or those with higher risk of bleeding.
- DNase are considered necessary to improve IPFT efficacy; however, in this case series, the use of intrapleural tPA alone produced good outcome.
- Optimal treatments for pleural infection are critical as it carries high mortality and morbidity. The use of intrapleural tPA alone for pleural infection is based on grade 2B evidence and should be used for those who do not respond to standard therapy, and who are not a candidate of video-assisted thoracoscopic surgery or surgical operations. Furthermore, since the introduction of intrapleural fibrinolytic agents, numbers of patients requiring surgery are fewer compared with the era before them.
- These patients should have a follow-up and repeated chest radiograph in 6–8 weeks' time.

this is the first two case reports describing the utility of 2.5 mg alteplase for loculated pleural effusion with positive outcomes.

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