



## Case report

## Short-course modified regimen intrapleural alteplase and pulmozyme (DNase) in pleural infection

M. Faisal<sup>\*</sup>, R. Farhan, X.K. Cheong, B.H. Ng, N. Nuratiqah, Ban Andrea YL

Respiratory Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Malaysia

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## ABSTRACT

Pleural infection is a common clinical condition leading to hospitalisation. In the last decade, advances in pleural research have led to a paradigm shift in the treatment of complex effusion from a surgical approach to a less invasive non-surgical approach using a combination of intrapleural fibrinolytics and pulmozyme (DNase). We report 3 patients with pleural infection. Intercostal chest catheter failed to drain the complex effusion. They were subsequently treated with a modified short-course regimen of alteplase and DNase. They received 3 cycles of 16 mg alteplase with 5 mg DNase each within 24 hours and all three had a favourable outcome with no adverse effects. This modified regimen appears effective with good safety profile and adds to the current literature on the safety and effectiveness of different dose combinations of alteplase and DNase.

## 1. Introduction

Pleural infection is a spectrum of disease caused by complicated parapneumonic effusion or empyema. Management of pleural infection involves adequate antibiotic therapy and drainage of infected fluid. In patients who failed chest tube, the use of intrapleural fibrinolytics and DNase can avoid the need for surgery. Fibrinolytic agents reported in the literature for management of pleural infection include alteplase, tenecteplase, urokinase, and streptokinase. The combination of tissue plasminogen activator (t-PA) alteplase 10 mg with DNase 5 mg have successfully improved fluid drainage and reduced the frequency of surgical referral and the duration of the hospital stay [1]. Due to the different formulation of alteplase in our centre; we use a modified regimen of alteplase 16 mg in combination with DNase 5 mg in 3 doses. This is to facilitate the utilisation of diluted medications within 24 hours [2]. This has proven to be successful, save and cost-effective in our centre. Patients' demographic data, clinical characteristics and laboratory investigations are summarised in Table 1.

## 2. Case presentation

## 2.1. Case 1

A 29-year-old man with no known medical illness presented with prolonged fever, cough and pleuritic chest pain for 3 days. On examination, he had reduced breath sounds and stony dullness over the right lung. He was febrile but otherwise had stable vital signs with oxygen saturation of 95% on 3L of oxygen. He had significant positive contact history with a colleague who was diagnosed with smear positive pulmonary tuberculosis.

Initial chest radiograph showed a right lower zone consolidation with pleural effusion (Fig. 1A). Septic parameters were raised and he had acute kidney injury (Table 1). He was started empirically on ceftriaxone 2g daily which was escalated to tazobactam/piperacillin 4.5g thrice daily in view of persistent fever. Intercostal chest catheter (ICC) was inserted which drained only 100 mls of serosanguinous fluid due to the presence of septations (Fig. 1B). Pleural fluid analysis was exudative in nature. Pleural fluid and bronchoalveolar lavage culture were sterile. The elevated pleural fluid adenosine deaminase of 64.8 U/L with pleural fluid lymphocytosis and positive Xpert® *Mycobacterium tuberculosis*/rifampicin assay confirmed the diagnosis of tuberculous pleural effusion; hence fixed-dose combination anti-tuberculosis (anti-TB); akurit-4

<sup>\*</sup> Corresponding author. Respiratory Unit, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, Bandar Tun Razak, 56000, Cheras, Kuala Lumpur, Malaysia.

E-mail addresses: [faisal.hamid@ppukm.ukm.edu.my](mailto:faisal.hamid@ppukm.ukm.edu.my) (M. Faisal), [radzinskovo@gmail.com](mailto:radzinskovo@gmail.com) (R. Farhan), [cheongxk@gmail.com](mailto:cheongxk@gmail.com) (X.K. Cheong), [ngboonhau@hotmail.com](mailto:ngboonhau@hotmail.com) (B.H. Ng), [kenix\\_atiqah@yahoo.com](mailto:kenix_atiqah@yahoo.com) (N. Nuratiqah), [andreaban@gmail.com](mailto:andreaban@gmail.com) (B. Andrea YL).

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**Table 1**  
Demographic and clinical characteristics of the patients.

Demographic data	Case 1	Case 2	Case 3
Sex	Male	Male	Male
Age (years)	29	76	54
Weight (kg)	60	57	62
Diagnosis	Tuberculous pleurisy	Empyema thoracis	Bacterial empyema thoracis with underlying pulmonary tuberculosis
Hematological and Infective Parameters			
White cell count ( $10^9/L$ )			
On admission	14.9	16.4	13.3
On discharge	8.0	10.8	11.5
Hemoglobin (g/dL)			
On admission	10.3	8.7	12.3
On discharge	9.5	9.2	11.0
C-reactive protein (normal < 5mg/dL)			
On admission	20.18	16.4	24.1
On discharge	5.01	0.84	7.6
HIV/Hep B/Hep C	Negative	Negative	Negative
Biochemical parameters			
LDH (normal <220U/L)			
On admission	110	124	205
Protein (g/dL)	62	65	66
Glycated haemoglobin (HBAIC %)	–	6.1	6.3
Pleural fluid analysis			
Site of effusion	Right	Right	Left
Appearance	serosanguinous	purulent	purulent
LDH (normal <220U/L)	872	8665	4914
Protein (g/dL)	59	43	57
Intercostal catheter (ICC)			
ICC size (Fr)	12	12	12
Duration of ICC (days)	5	8	7
Pleural drainage post IPFT (mls)			
Day 1	220	260	500
Day 2	1100	500	650
Day 3	340	650	1110

was started and antibiotic was withheld.

We decided for intrapleural fibrinolytic therapy (IPFT) and he received 3 doses of alteplase 16 mg and DNase 5 mg in 24 hours. There was an increase in daily drainage from 220 mls to 1100 mls and 340 mls. The patient's cough improved and his fever subsided. Both chest radiograph and thoracic ultrasound imaging showed improvement of the effusion (Fig. 1C and D), and he was discharged well and completed 6 months of anti-TB.

## 2.2. Case 2

A 76-year-old man with underlying diabetes and hypertension was referred for further management of a complex pleural effusion and liver abscess. He gave a two-week history of right-sided pleuritic chest pain and hypochondriac pain, lethargy, loss of appetite and weight. On examination, he was febrile with stable vital signs. Oxygen saturation was 95% on 3 L of oxygen. He had reduced breath sound and stony dullness over the right lung and hepatomegaly with liver span of 14 cm.

The infective blood parameters were raised (Table 1). Chest radiograph revealed right-sided loculated effusion (Fig. 1E). Computed tomography (CT) thorax revealed a multi-loculated right pleural collection with collapse consolidation of apicoposterior segment of the right upper lobe with liver abscess (Fig. 1F). As he had completed 10 days of amikacin 750mg daily and meropenem 1g thrice daily at his previous hospital, he was commenced on tazobactam/piperacillin 4.5g

thrice daily in our centre.

ICC was inserted which drained only 100 mls purulent fluid overnight. Pleural fluid analysis revealed exudative effusion with pleural LDH of 8665 IU/L (Table 1). Pleural fluid and liver abscess were drained and culture grew *Klebsiella pneumoniae*. He was treated as invasive *Klebsiella* syndrome and antibiotic was de-escalated to amoxicillin/clavulanate group based on sensitivity. Three courses of intrapleural alteplase 16 mg with DNase 5 mg were administered as per our protocol to facilitate pleural drainage. Significant drainage was achieved subsequently which led to improvement of infective blood parameters, and imaging (Fig. 1G and H).

In view of the persistent liver abscess, he completed 28 days of intravenous amoxicillin/clavulanate and 6 weeks of oral amoxicillin/clavulanate. He remained well on follow up.

## 2.3. Case 3

A 54-year-old man with underlying diabetes, hypertension, and smear negative pulmonary tuberculosis (diagnosed via positive sputum Xpert® *Mycobacterium tuberculosis*/rifampicin assay) on day 56 of intensive phase therapy was referred to our centre for further management of a complex left pleural effusion. Clinically he was tachypnoeic with a respiratory rate of 30/minute, heart rate of 110/minute and febrile at 38 °C. Oxygen saturation was 93% on 3L of oxygen.

The infective blood parameters were raised (Table 1). Chest radiograph revealed left moderate pleural effusion (Fig. 1I). CT thorax showed multifocal empyema and lung abscess (Fig. 1J). Blood and pleural culture were negative. He was started on tazobactam/piperacillin which was escalated to meropenem after 72 hours in view of persistent fever and raised infective parameters.

ICC was inserted which drained minimal amount of purulent fluid. Pleural fluid analysis are listed in Table 1.

IPFT was decided; he received 3 doses of alteplase 16 mg and DNase 5 mg as per our protocol. Subsequent drainage increased to 1.1 L. The fever and breathlessness resolved and there was improvement of infective parameters. Chest radiograph (Fig. 1K) showed improvement of the effusion. He was discharged with amoxicillin/clavulanate 625 mg thrice daily for 4 weeks and maintenance therapy of anti-TB. A repeat CT thorax done on follow-up in clinic a month later, showed complete resolution of empyema (Fig. 1L).

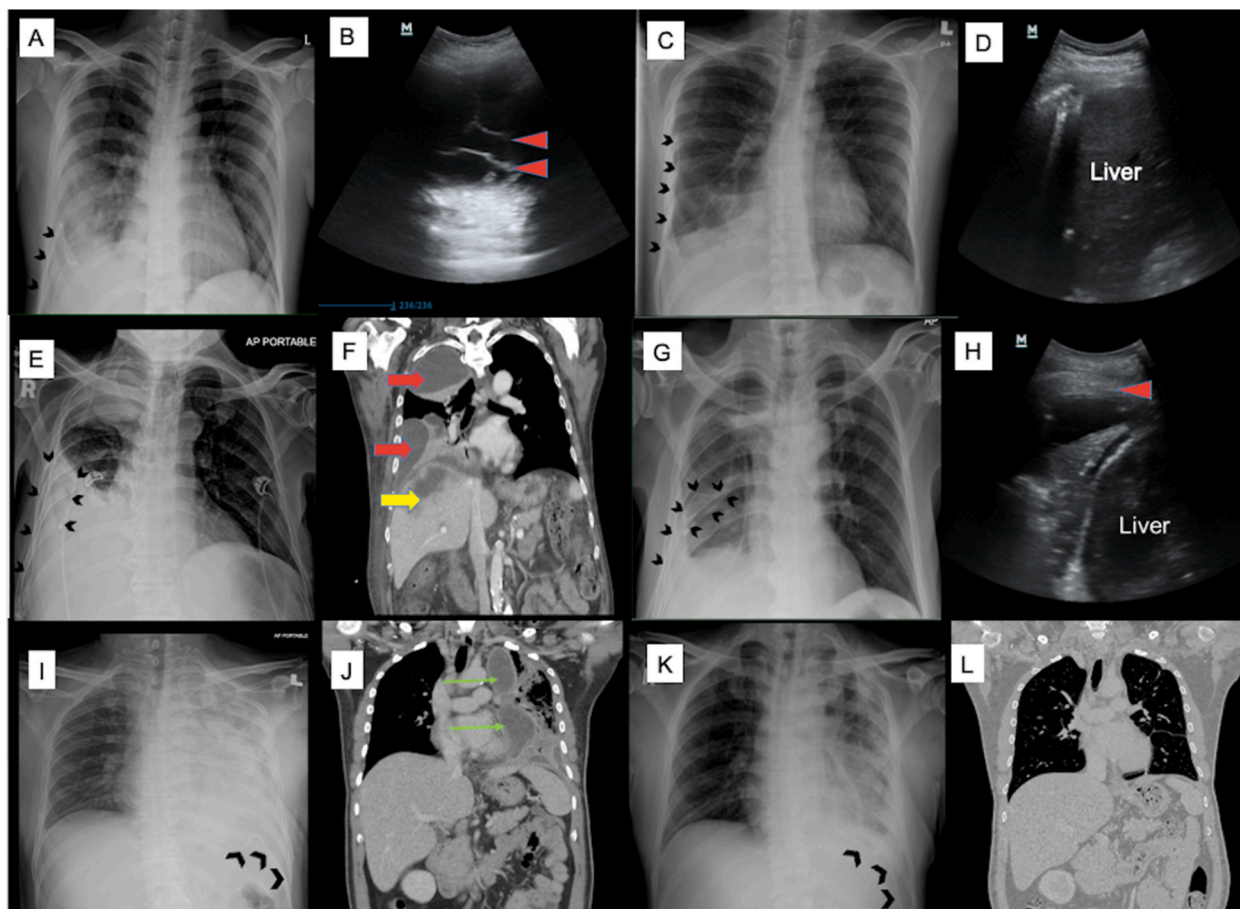
## 3. Discussion

Parapneumonic effusion can be divided in exudative, fibrinopurulent and organising stage. When inadequately treated, they may progress to fibrinopurulent stage with pleural pH < 7.2, LDH > 1000 IU/L, glucose < 2.2 mmol/L [3,4]. When this occurs, there is deposition of fibrin clots and fibrin membranes in the pleural cavity, leading to fluid loculations [3,4]. This can progress further to an organising stage where the fibrin membranes are transformed into a thick non-elastic pleural peel by the fibroblast, resulting in trapped lung [3,4].

IPFT is a useful adjunct in the therapy during fibrinopurulent phase. Based on our case series, administration of IPFT was effective in facilitating the drainage of pleural fluid; improving radiological imaging and inflammatory parameters and shortening the duration of chest drain to an average of 6.5 days.

There has been extensive research and publication on the combination of intrapleural alteplase and DNase. Different studies have demonstrated effective doses of alteplase ranging from as low as 2.5–50 mg/day [1,2,5–9]. In our case series, we used 3 doses of intrapleural alteplase 16 mg per instillation 8 hours apart over 24 hours. The medication was diluted in 50 mls and after instillation, it was allowed to dwell for 45 minutes before releasing the drainage for a subsequent 45 minutes. The process was repeated with intrapleural DNase with dosage of 5 mg.

The dose of 16 mg alteplase was chosen to maximise its utilisation



**Fig. 1.** Patient 1: Chest radiograph (A) showed right moderate pleural effusion with ICC in situ (black arrows). Thoracic sonography (B) with red arrows showed multiple septations. Chest imaging (C) and repeated thoracic sonography (D) post IPFT showed resolution of the effusion. Patient 2: Chest radiograph (E) showed moderate effusion with ICC in situ (black arrows) and CT thorax (F) showed multiple loculated pleural effusion (red arrows) with liver abscess (yellow arrow). Repeated chest radiograph (G) and thoracic sonography (H) post IPFT showed minimal unilocular right effusion with pleural thickening (red arrow). Patient 3: Chest radiograph (I) showed moderate left effusion (black arrow) and CT thorax (J) showed multiloculated empyema and lung abscess (green arrow). Repeated chest radiograph (K) post IPFT showed improvement (black arrows – outline of ICC). CT thorax (L) on follow-up in clinic showed complete resolution of empyema.

per day and to reduce drug instability after 24 hours of dilution; as the formulation of alteplase in our centre was 50 mg per vial [2]. This dose allows 3 instillations of 16 mg alteplase within 24 hours in combination with DNase. Our method differs slightly from Abu-Daff et al. who used 16 mg alteplase monotherapy daily for 3 days in their patients [5]. We chose to instill intrapleural alteplase 8 hourly with the understanding that t-PA has a short half-life of 3–6 minutes with low systemic absorption and bleeding risk [10]. Rahman et al. in MIST-2 trial reported 5 patients (6%) who developed bleeding. This included 1 patient with hemoptysis and 2 with intrapleural bleed [1]. None of our 3 patients developed systemic and pleural bleeding or significant drop in haemoglobin levels. Pain, which is a common side effect of intrapleural fibrinolysis were mild and tolerable in our patients.

In our first case, the instillation of intrapleural fibrinolysis in TB empyema increases fluid output via chest drain and associated with clinical and radiological improvement. Although there is limited evidence to support the use of TPA and DNase in TB empyema/pleuritis, we have shown success as demonstrated in patient 1. Similar success was seen in the other patients with pleural infection. There was marked pleural drainage as early as the first day of its administration and this was followed by a good recovery evidenced by amelioration of the inflammatory markers and resolution of fever.

In conclusion, administration of IPFT is a useful adjunctive therapy in the treatment of pleural infection. The optimal dose of intrapleural

alteplase is still unknown and varies with different centres. We demonstrated the efficacy and safety of intrapleural alteplase of 16 mg with DNase of 5 mg in our cohort. We are currently conducting a larger prospective study to demonstrate the efficacy and acceptable safety profile of this regimen.

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