



## Case report

# Low dose intrapleural alteplase and pulmozyme (DNase) in two post-surgical patients with pleural sepsis

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## ARTICLE INFO

## Keywords:

Alteplase  
DNase  
Intrapleural fibrinolytic  
Pleural infection  
Post surgery

## ABSTRACT

Alteplase and pulmozyme (DNase) administered intrapleurally have revolutionised the management of pleural infection in the last decade. However, the use of intrapleural fibrinolytic has not been well established in high risks patients. Here, we describe 2 patients with high risk of bleeding due to recent surgery who developed empyema; successfully treated with these medications. The first patient was a 36-year-old female post oesophagectomy for oesophageal carcinoma, complicated with anastomotic leak and empyema; and the second patient was a 56-year-old female post percutaneous nephrolithotomy for right obstructive uropathy who developed right-sided empyema. Both patients were treated successfully with 3 doses of intrapleural alteplase 2.5 mg and DNase 5 mg without any major adverse effects. This case report adds to the current literature on the safety of intrapleural fibrinolytics and highlights that lower doses of alteplase in combination with pulmozyme is efficacious and may be considered in high-risk patients.

## 1. Introduction

Pleural infection is a common problem requiring evaluation, adequate antimicrobials and therapeutic intervention. As it progresses to the fibrinopurulent stage, the free-flowing fluid becomes viscous with the presence of locules or septations which leads to inadequate drainage. In such instances, the combination of intrapleural alteplase and DNase may be used as an alternative to surgical intervention [1,2]. Alteplase degrades the fibrin matrix of thrombus that breaks down fibrin clots leading to lysis of the pleural adhesions. DNase cleaves the deoxyribonucleic acid (DNA) from the leucocyte degradation and makes the pus less viscous [3]. The combination of both alteplase and DNase improves fluid drainage. Rahman et al. demonstrated the combination of 10 mg alteplase with 5 mg DNase reduced surgical referral, length of stay and improved fluid drainage [4]. Pleura and systemic bleeding rate were reported around 4.1% and 6.3% [4]. As both patients had recent surgery, we opted for dose de-escalation of 2.5mg alteplase (2.5mg) with 5mg DNase to minimise the risk of bleeding. Both patients had positive outcomes without any sequelae.

## 2. Case 1

A 36-year-old non-smoker presented with a 2-month history of progressive dysphagia, constitutional symptoms and significant weight loss. Oesophageal-gastro-duodenoscopy (OGDS) revealed a mid-oesophageal circumferential tumour and biopsy showed moderately differentiated squamous cell carcinoma. Computed tomography (CT) scan of the thorax, abdomen and pelvis (TAP) revealed a large segment thoracic oesophagus circumferential mass with no distant metastasis. Positron emission tomography (PET) CT Scan confirmed the staging at Stage IIIA.

She underwent a total laparoscopic thorascopic oesophagectomy which was complicated by a right pneumothorax, nosocomial pneumonia and an anastomotic leak of the oesophagus. She was treated with antibiotics, a 24 Fr right chest drain and 2 mega-stents to the oesophagus. Bronchoscopy showed no evidence of tracheoesophageal fistula and the bronchioalveolar lavage was culture-negative.

Both blood and sputum culture grew *Pseudomonas aeruginosa*. She developed a pleural effusion which was culture-negative and exudative. A CT thorax revealed a rim enhancing pleural collection with presence of air pockets within suggestive of empyema. We reinserted a 28F chest drain which failed to drain the fluid. We then decided to use intrapleural fibrinolysis.

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<https://doi.org/10.1016/j.rmcr.2020.101111>

Received 25 May 2020; Accepted 27 May 2020

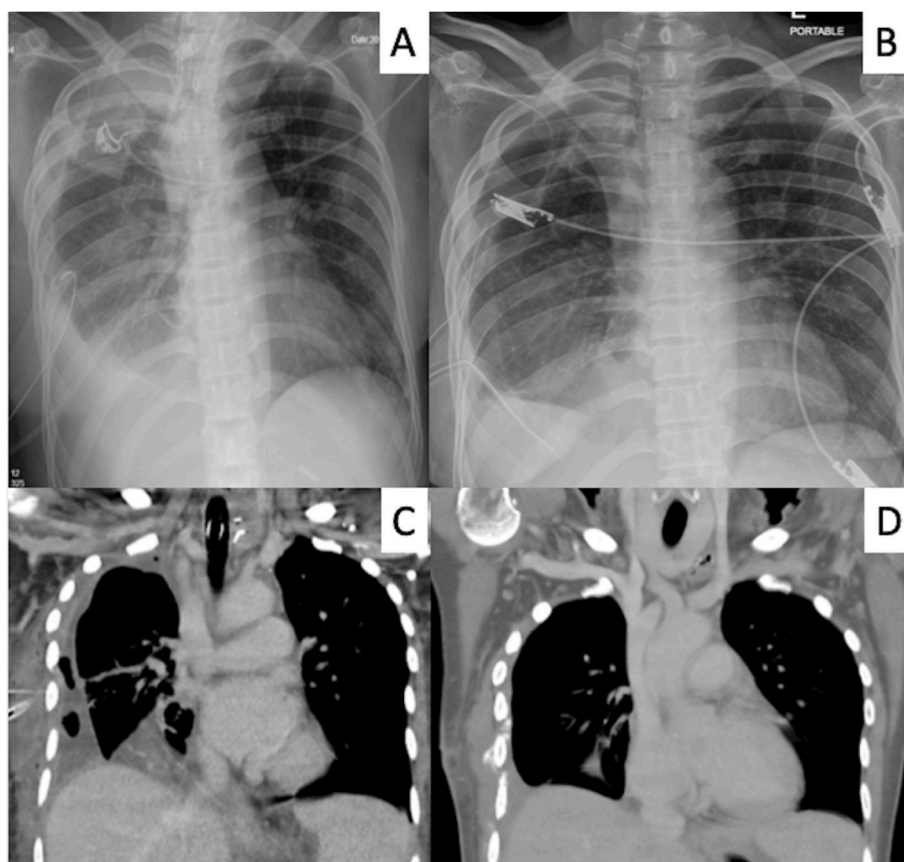
Available online 29 May 2020

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**Fig. 1.** Chest radiograph (A) before intra-pleural alteplase and DNase showing right sided effusion (B) post 3 doses intra-pleural alteplase and DNase with resolution of right sided effusion. CT Thorax (C) before intrapleural fibrinolysis and (D) 2 weeks post Intrapleural fibrinolytics showing successful resolution of right sided empyema.

She received a total of 3 doses of intrapleural 2.5mg alteplase with 5 mg of DNase with no major adverse events. A total of 1.6L was drained and serial chest radiographs (Fig. 1A and B) and CT Scans (Fig. 1C and D) showed significant improvement. She was discharged well.

### 3. Case 2

A 68-year-old woman, with underlying hypertension, presented with haematuria and was diagnosed with bilateral staghorn renal calculi with bilateral hydronephrosis. She underwent an initial bilateral ureteric stenting followed by a right percutaneous nephrolithotomy (PCNL). Post-operatively, she developed nosocomial pneumonia which developed into a right parapneumonic effusion requiring non-invasive ventilation (Fig. 2A). Bedside thoracic ultrasonography revealed the presence of a complex effusion.

We inserted a 12 Fr intercostal tube under ultrasound guidance. Pleural fluid was exudative and culture-negative. Pleural to serum creatinine ratio was <1 indicating no evidence of nephro-pleural fistula. She was treated with broad spectrum antibiotics.

Due to the minimal drainage, we decided to administer 3 doses of intrapleural 2.5mg alteplase and 5 mg DNase. She had no major adverse events. A total of 2.1L of haemoserous fluid was drained and serial chest X-rays (Fig. 2B and C) showed significant improvement. The chest drain was removed after 3 days and she was discharged well.

### 4. Discussion

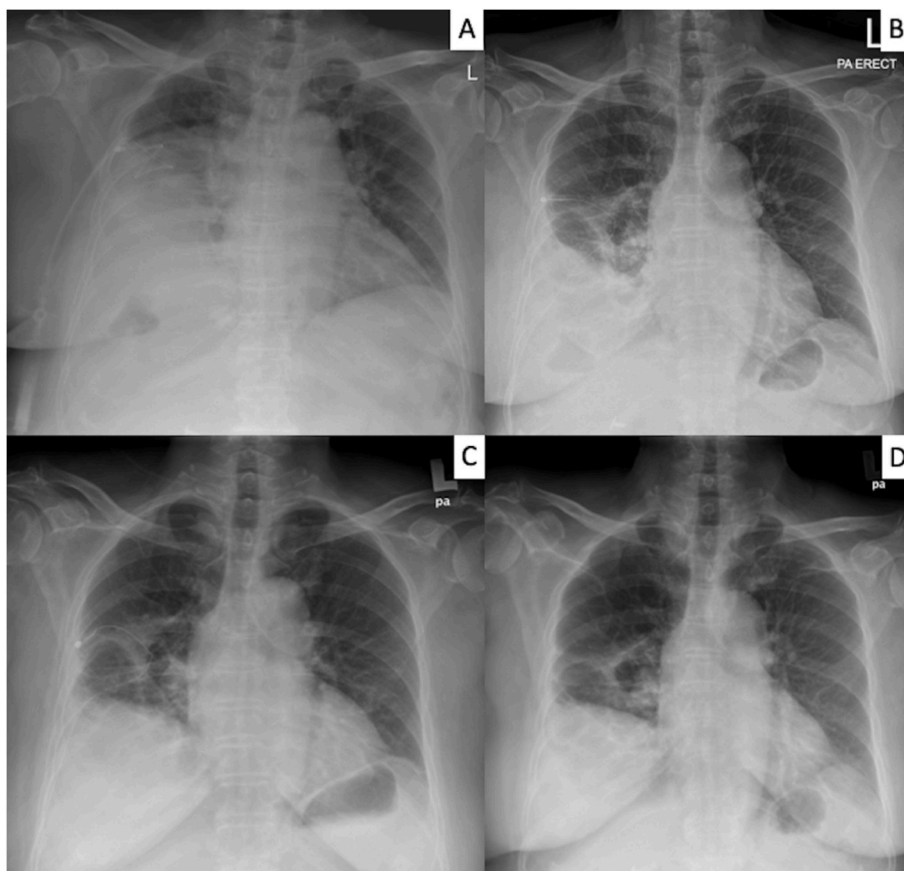
Pleural effusion can be categorised into three different spectrums; exudative phase, fibrinopurulent phase and empyema. The treatment requires drainage of the fluid at all three stages. When the effusion

progresses into the fibrinopurulent phase or empyema, drainage may not be possible as septations or loculations may developed within the effusion. Hence, medical treatment with alteplase and DNase may be instituted as an alternative to surgery.

Both cases showed drainage failure of the empyema regardless of the size of the chest drain. In the first case, chest tube sizes 24 Fr and 28 Fr were used and in the second case, a 12 Fr chest drain was used. Prior to availability of DNase in our centre, we used alteplase monotherapy to treat complex effusion [5–7]. Our current practice is a combination of both medications based on the MIST-2 trial.

A wide range of dosing of alteplase; e.g. 4–100mg has been reported [4,8,9]. The question of the lowest effective dose of alteplase to be used with DNase is still not known. Rahman et al. in MIST 2 used combination of 10 mg TPA (alteplase) with 5 mg of DNase [4]. There are few other studies using lower doses of alteplase; e.g Popowicz et al. reported 5 mg alteplase with 5 mg of DNase showed similar efficacy with 10 mg alteplase [10]. Hugh et al. used 2.5 mg of alteplase with 5 mg of DNase also found similar efficacy compared with 10 mg alteplase [11]. Based on these studies, we decided to use 2.5 mg alteplase with 5 mg DNase in both of our patients. Our decision to use low-dose 2.5 mg alteplase with 5 mg DNase in both patients was due to the fact that both were at higher risk of bleeding as they had recent surgery. Although systemic bleeding incidence with 10 mg of alteplase from combined patients in studies by Rahman, Majid, Mehta, Piccolo and Popowicz et al. were reported low at 0.8%, these patients did not have any recent surgery performed [4,10,12–14]. Recently, the lowest dose reported dose of alteplase was 0.5 mg, used with success in a coagulopathic patient with deranged liver enzyme who had blocked indwelling pleural catheter [15].

Both patients received tramadol 15–20 minutes before procedure. Sequential alteplase at 2.5 and DNase 5 mg were instilled intrapleurally.



**Fig. 2.** A schematic diagram showing serial chest radiographs; (A) Before treatment with a moderate right sided pleural effusion, (B) Day 1 post, (C) Day 3 post, (D) Day 5 post intra-pleural alteplase and DNase. This diagram demonstrates the significant improvement of the complex right pleural effusion.

Following each medication the drain was clamped for 45 minutes and drained for a further 45 minutes. The cycle of alteplase and DNase was repeated 12 hourly and both patients received a total of three cycles with no adverse effects.

We used three instead of six doses because of the formulation preparation of alteplase. In Malaysia, alteplase comes in 50 mg formulation. Once diluted, the compound remains stable for 24 hours allowing only 3 doses 12 hourly. Alteplase is a costly medication and using a lower-dose may translate to cost savings.

We opted for sequential rather than concurrent instillation of intrapleural alteplase and DNase. Majid et al. reported the success of concurrent alteplase and DNase, e.g combination of both alteplase and DNase intrapleurally without interval [13]. This may save total time of intrapleural instillation. However, it should be emphasised the patients who received concurrent alteplase and DNase in that study were given medications much earlier (within 24 hours) as compared by patients in the study by Piccolo et al. [12] who received treatment after 24 hours; hence the author postulated that the success of concurrent alteplase and DNase might be influenced by the earlier referral and administration of intrapleural medication. Until more studies are available, we will continue to practise sequential alteplase and DNase in our centre as the majority of our patients are referred late to pleura consultant.

We conclude that the combination of lower dose of alteplase e.g 2.5 mg with DNase 5 mg is efficacious in improving fluid drainage and decreasing length of hospital stay without any adverse side effects and should be considered in patients who are at higher risk of bleeding.

#### Author's contribution

Mas Fazlin and Mohamed Faisal was involved with the concept,

acquisition of data and drafting of manuscript. Ng Boon Hau and Nik Nuratiqah was involved with literature of review. Andrea Ban and Mohamed Faisal contributed to critical revision of important intellectual content. All authors had full access to data, contributed to the paper, approved the final revision for publication and take responsibility for its accuracy and integrity.

#### Funding

The paper did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Written informed consent was obtained from the patient to publish this case report and the accompanying images.

#### Declaration of competing interest

The authors declare that they have no competing interests.

## Acknowledgments

The authors would like to thank Dean of Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Professor Dr Raja Affendi Raja Ali for permission to publish this case.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2020.101111>.

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