

Case Report

Clinical Response-Guided tPA and DNase Administration as Rescue Treatment for Postoperative Empyema

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ABSTRACT

Empyema untreated carries significant mortality. Medical management with tube thoracostomy accompanied by combination therapy with intrapleural tissue plasminogen activator (tPA) and deoxyribonuclease (DNase, dornase alpha) has decreased the need for surgical intervention. Most studies on this combination therapy have been done on empyema associated with community acquired pneumonia. A fixed regimen of tPA and DNase has a high cost and carries a small risk of intrapleural hemorrhage. We report on two patients who developed empyema postoperatively. Intrapleural DNase and tPA were administered concurrently at a frequency and duration based upon the clinical response. Both patients had successful outcomes without adverse effects.

INTRODUCTION

The incidence of empyema is increasing worldwide. Untreated, empyema carries a 20% mortality.¹⁻⁴ Primary management involves antibiotics and tube thoracostomy. Empyema with increased pleural fluid viscosity and the presence of loculations may be refractory to this approach. Refractory empyema is treated with surgical decortication and drainage, an approach associated with increased hospitalization. An alternative to surgery is tube thoracostomy followed by the administration of intrapleural tPA and DNase twice a day for three days. tPA, through the generation of plasmin,^{*} helps to breakdown loculations. DNase decreases pleural fluid viscosity by digesting free deoxyribonucleoprotein from leukocyte degradation.

tPA and DNase are expensive and may cause adverse effects, notably intrapleural hemorrhage. Administration of either one of these drugs alone has not been shown to be beneficial.^{5,6} Observational studies have shown that the administration of this combination therapy according to clinical response does not change efficacy.

There are no specific studies addressing tPA/DNase treatment of empyema which formed in the late postoperative period. We report two postoperative empyema cases treated successfully with late administration (after over 48 hours of chest tube drainage) with intrapleural combination therapy.

* tPA converts plasminogen to plasmin, a member of the serine protease family (which includes trypsin). Plasmin proteolyzes numerous proteins including fibrin and fibronectin. It also activates collagenases.

Case 1

A 68 year old woman with alcohol abuse and a 12 pack-year history of cigarette smoking was found to have a spiculated 1.4 cm right upper lobe nodule. She underwent elective video assisted thoracoscopy for a right upper lobe wedge resection. Her hospitalization was complicated by alcohol withdrawal, prolonged mechanical ventilation requiring a tracheostomy, acute blood loss from tracheal erosion, and acute kidney injury requiring hemodialysis. On postoperative day thirty, she was noted to have increasing right-sided consolidation, a pleural effusion, and persistent leukocytosis.

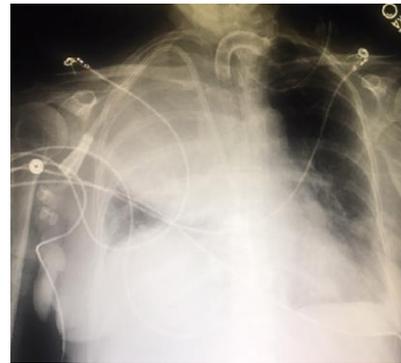


Figure 1. Initial chest radiograph of the showing the left-sided loculated pleural effusion.

A pigtail catheter (14 Fr) was placed. Pleural fluid studies showed cloudy fluid, glucose < 10 mg/dL, LDH 11,119 U/L, total protein < 3 g/dL, pH 6.9, WBC 300,000 cells/ μ L, RBC 101,000 cells/ μ L, neutrophils 95%, cholesterol 78 mg/dL, and amylase 36 mg/dL. Piperacillin-tazobactam and vancomycin were administered.

After 48 hours, the chest tube drainage decreased from 800 mL to 150 mL/24 hours. There was no radiographic improvement of the pleural effusion. Due to hemodynamic instability, the patient was at high risk for surgery. This prompted treatment with intrapleural tPA 10 mg and DNase 5 mg administered together. The drainage increased from 150 mL to 570 mL per 24 hours. After four days, the drainage de-

creased to 120 mL per day. A second dose of tPA 10 mg and DNase 5 mg was given. The chest tube drainage increased to 300 mL per day. The pleural fluid culture was positive for *Gemella morbillorum*. Her antibiotic regimen was changed to cefoxitin.



Figure 2. Radiograph of the chest showing almost complete resolution of the pleural effusion after drainage, antibiotics, and rescue administration of intrapleural tPA and DNase.

The pleural drainage subsequently diminished and there was radiographic improvement of the pleural effusion. The pleural drainage transitioned from frank pus to serosanguinous fluid. The chest tube was removed after 10 days. The patient was discharged to long term acute care (LTAC).

Case 2

A 70 year old man was admitted with septic shock. He had a prior history of diabetes mellitus type 2, systolic heart failure with an ejection fraction of 20%, an AICD implant, atrial fibrillation, asthma, interstitial lung disease with fibrotic changes in the lower lobes, GERD, and sleep apnea. He had undergone elective gastric bypass surgery two months prior to admission.

Pertinent laboratory findings included white blood cell count (WBC) $12.7 \times 10^3/\mu\text{L}$ and lactic acid 2.8 mmol/L. Computerized tomography of the chest, abdomen and pelvis showed fibrotic changes in the lower lobes, a loculated left-sided

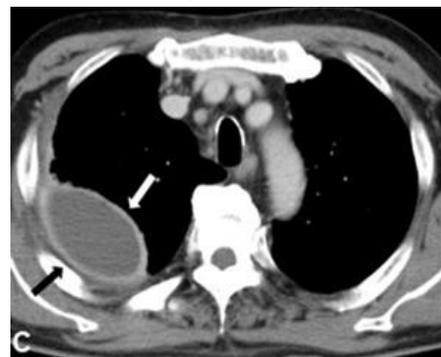
pleural effusion without split pleura sign^{***} and a heterogenous 8.9 x 8.7 x 8.6 cm soft tissue mass in the left upper quadrant. He was started on cefepime and vancomycin.



Figure 3. Initial computerized tomographic image showing the left-sided located pleural effusion.

A pigtail catheter (Fr 14) was inserted into the left-side pleural effusion. The pleural fluid studies showed cloudy fluid, glucose < 10 mg/dL, LDH 1,129 U/L, protein 4.5 g/dL, pH 6.4, WBC 90,790 cells/ μL , RBC 17,000 cells/ μL , neutrophils 97%, cholesterol 71 mg/dL, and amylase 36 mg/dL. The pleural fluid culture was positive for pan-sensitive *E. coli*. The patient refused surgery. After chest tube insertion, tPA 10 mg and DNase 5 mg were instilled together intrapleurally twice daily for three days.

*** Split Pleura Sign: Thickened visceral and parietal pleura separated by fluid.



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The abdominal fluid collection was also drained. It showed cloudy fluid. Its culture was positive for pan-sensitive *Escherichia coli*, *Streptococcus viridans*, and *Prevotella oralis*. After five days of small bore tube thoracostomy drainage, persistent leukocytosis and drainage purulence prompted the insertion of a large bore (28 Fr) chest tube. Eleven days after the insertion of the initial chest tube, the patient had persistent leukocytosis and decreasing chest tube drainage. Chest computerized tomography showed a worsening loculated pleural effusion.

A 7th and 8th dose of tPA 10 mg and DNase 5 mg were given. Based on the chest tube output and the character of the fluid, they were instilled together 12 hours apart. The chest tube output increased from 20 mL to 500 mL. Its character changed from pus to serosanguinous. Leukocytosis normalized.

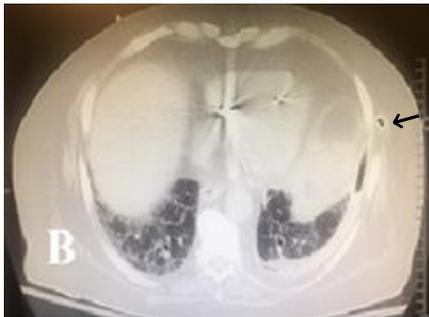


Figure 4. Final computerized tomography of the chest showing the 28 Fr chest tube and almost complete resolution of the pleural effusion after drainage, antibiotics, and rescue administration of intrapleural tPA and DNase.

On day 13, after the output was < 20 mL/24 hours and chest computed tomography showed resolution of the empyema collection, the 28 Fr chest tube was removed.

The patient was discharged to a rehabilitation facility.

Discussion

In the treatment of empyema, intrapleural medication via chest tube may be as efficacious as video-assisted thoracoscopy.^{5,7} The sequence, duration, and frequency of intrapleural medications have been investigated.

Rahman et al.'s⁵ double blinded, double dummy, randomized trial comparing placebo, tPA only, DNase only, and tPA plus DNase showed that sequential intrapleural administration of tPA 10 mg and DNase 5 mg twice a day for three days improved pleural drainage, decreased surgical referral, and decreased inpatient stay.

The change in pleural opacity in tPA/DNase was greater than placebo ($-29.5 \pm 23.3\%$ vs $-17.2 \pm 9.6\%$; difference -7.9% confidence interval -13.4 to 02.4 ; $p = 0.005$). The change after either tPA or DNase alone did not differ significantly from placebo.

Surgical referrals were decreased in the tPA/DNase group as compared to placebo (2 of 48 patients [4%] vs. 8 of 51 patients [16%]). There was a reduction in the duration of hospital stay with combination therapy versus placebo (difference -6.7 days; 95% CI 12 to -1.9 ; $P = 0.006$). Single agent treatment alone was not significantly different from placebo.

Patient categories that were excluded in the Rahman study were < 18 years of age, prior treatment with an intrapleural fibrinolytic agents, DNase, or both for empyema, DNase or tPA sensitivity, co-incidental CVA, major hemorrhage or major trauma, major surgery in the previous five days, previous pneumonectomy on the infected side, pregnancy, and expected survival of < 3 months. Small bore chest tubes (< 15 Fr) were used.

Since then, variations of intrapleural therapy have been explored. In Majid's retrospective cohort, concurrent administration of tPA and DNase within one day of insertion of a small bore (< 14 Fr) chest tube in patients with empy-

ema and complicated parapneumonic pleural effusions improved drainage.⁸ Decreased drainage (< 200 mL/24 hours) and radiographic evidence of loculations on chest ultrasound or CT scan determined the timing of the tPA and DNase. The chest tubes were removed on day 5 and the patients were discharged after day 11.⁸ Kheir corroborated this concurrent administration of tPA and DNase as a safe and effective option.⁹

A study by McClune et al.¹⁰ showed that extended use of this intrapleural therapy was safe and effective for pleural space infections. A series of multinational observational studies^{11,12} evaluated the combination of tPA and DNase as a “rescue” intervention for community acquired pneumonia if there was no improvement after 24 hours of treatment with antibiotics and tube thoracostomy. Most of the patients had a small (<16 Fr) chest tube. Some of the centers gave the tPA and DNase sequentially while others gave the medications concurrently. 92.3% of patients were treated successfully. Two patients (1.8%) had intrapleural hemorrhage. Both patients had an underlying coagulopathy.¹¹ Mehta et al.¹³ administered this combination once a day within 24 hours of tube thoracotomy sequentially. Fifty-one patients (92.7%) were successfully managed without surgical intervention. There was no report of bleeding. 12 - 14 Fr chest tubes were used. **

Pleural hemorrhage occurs in 1.8 - 12% with intrapleural tPA.^{8,14,15-19} Popowicz’s multinational, open label study showed that tPA 5 mg / DNase 5 mg twice a day suggested non-inferiority to tPA 10 mg / DNase 5 mg twice a day with comparable both of avoidance of sur-

gery and of improved 30 day survival with a reduced incidence of intrapleural hemorrhage.²⁰ 93% of the patients received this combination therapy >24 hours after tube thoracotomy, 39% of those received it >48 hours.²⁰ 59% of the patients had chest tube size 12 Fr, 16% of patients had 18 Fr, and 6.5% had 32 Fr.²⁰ However, 4.9% of the patients had intrapleural hemorrhage requiring transfusion.²⁰

In our two patients, the frequency and duration of the tPA and DNase administration was based on their clinical response which was determined by the change in leukocytosis, fever, radiographic evidence of a decrease in effusion, the volume of pleural fluid drained per 24 hours, and the pleural fluid characteristics. We consider this approach a “rescue” intervention since the medications were given >2 days after chest tube insertion. In one of our patients, two additional doses were given >11 days after the initial chest tube insertion and after a failed response to the initial three days of combination therapy. There were no episodes of hemorrhage or other adverse effects.

tPA/DNase combination therapy is an important option for patients with late postoperative empyema who are poor surgical candidates or who decline surgery. The frequency and duration of treatment can be based on the clinical response without compromising efficacy or increasing adverse effects. This scheme minimizes medication cost. Randomized controlled trials of this combination in empyema in patients who are at least thirty days postoperative are warranted.



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** TPA was instilled. The chest tube was clamped for one hour and unclamped for one hour to allow drainage under -20 cm H₂O suction. This was followed by instillation of DNase administered in the same fashion.

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