# Fibrinolysis Treatment for Parapneumonic Pleural Effusion with Intrapleural Tissue Plasminogen Activator

# İntraplevral Doku Plasminojen Aktivatörüyle Parapnömonik Plevral Efüzyon için Fibrinoliz Tedavisi

**Gürbüz Akçay[1], Nazile Ertürk[2], Aynur Köş[1], Arife Zeybek[3], Önder Yeniçeri[4]**

[1]Mugla Sitki Kocman University Research and Training Hospital, Department of Pediatrics, Mugla,Turkey
[2]Mugla Sitki Kocman University Research and Training Hospital, Department of Pediatric Surgery, Mugla,Turkey
[3]Mugla Sitki Kocman University Research and Training Hospital, Department of Chest Surgery, Mugla,Turkey
[4]Mugla Sitki Kocman University Research and Training Hospital, Department of Radiology, Mugla,Turkey

**Abstract**
Intrapleuritic fibrinolytic agent administration is an alternative treatment option in some patients. The ideal candidates include those who have an unfavourable general status for surgery or who fail to show adequate improvement despite standard therapy (e.g chest tube insertions, pleurodesis). Unfortunately, as an alternative treatment approach, fibrinolytic agent administration is not offered to patients as often as desired. In this paper, a seven-year-old male with parapneumonic pleural effusion following right lower lobe pneumonia was reported. The patient showed minimal improvement after insertion of a chest tube and administration of wide-spectrum antibiotic therapy whereas intrapleural loculations and septations persisted. Therefore, tissue plasminogen activator (tPA) was administered into the intrapleural space daily for three consecutive days. After the treatment, the loculations were resolved, fluid drainage was facilitated, and significant radiological and clinical improvement followed. In conclusion, tPA treatment provides favorable results in patients with parapneumonic pleural effusions that are unsuitable for surgery or unresponsive to standard therapy.
**Keywords:** Children, Empyema, Fibrinolysis, Parapneumonic Effusion, Pleural Effusion, Tissue Plasminogen Activator

**Özet**
İntraplevral fibrinolitik ajan uygulaması bazı hastalarda alternatif bir tedavi seçeneğidir. Ya hastanın genel durumu cerrahiye uygun değildir, ya da standart tedaviye rağmen (örneğin göğüs tüpü konulması, pleurodesis) iyileşme sağlanamamıştır. Ne yazık ki, fibrinolitik ajan uygulaması pratikte alternatif bir tedavi yaklaşımı olarak beklendiği kadar sunulmaz. Çalışmada, sağ alt lob pneumonisi sonrası oluşan parapneumonic pleural effusionu olan yedi yaşında erkek hasta sunulmuştur. Hasta, göğüs tüpü yerleştirilmesi ve geniş spektrumlu antibiyotik tedavisinden sonra minimal iyileşme gösterdi. Fakat intraplevral lokulasyon ve septasyonlar devam etti. Bunun üzerine arka arkaya üç gün boyunca günlük doku plazminojen aktivatörü (tPA) intraplevral olarak uygulandı. Tedavi sonrası lokülasyonlar azaldı, drenaj kolaylaştı, önemli radyolojik ve klinik iyileşme izlendi. Sonuç olarak cerrahi müdahaleye uygun olmayan veya standart tedaviye yanıt vermeyen parapneumonic pleural effusionu olan hastalarda tPA tedavisi başarılı sonuçlar vermektedir.

**Anahtar Kelimeler:** Çocuk, Ampiyem, Fibrinolizis, Parapnömonik Effüzyon, Plevral Effüzyon, Doku Plazminogen Aktivatörü

Başvuru Tarihi / Received: 25.11.2016
Kabul Tarihi / Accepted : 01.06.2017

## Introduction

In children, parapneumonic effusion is a complication of bacterial pneumonia in about 0.6% to 2% of cases (1). Effective antibiotic therapy empyema is fatal in 5% of children. The majority of pneumonia- associated pleural effusions improve by the treatment of primary infection, although surgical intervention is required in 10% of cases. Fibrinolytic agent administration is an alternative to surgical therapy. In this paper we report pediatric patients with parapneumonic pleural effusion that favorably responded to intrapleural tPA (tissue plasminogen activator) administration; we also provided a review of the relevant medical literature.

## Case

A 7-year-old boy was referred to our outpatient clinic by an outside center for further workup of acute abdomen. The patient had diffuse abdominal pain for 24 hours but had no other symptoms.

On physical examination he had a body temperature of 38°C, heart rate of 88 bpm at the point of maximal impulse, and respiratory rate of 37 breaths per minute. He appeared weak and pale. On respiratory examination he had nasal flaring and intercostal and suprasternal retractions. On auscultation there were fine crackles over the basal fields of his right lung. He had pain over his right hemithorax upon palpation. His abdominal examination was free of guarding, tenderness, or signs of organomegaly. A posteroanterior chest X-Ray (CX-R) (Figure 1) revealed an infiltration of the right lower lobe and, additionally, scoliosis of thoracic vertebrae. Based on the above findings, he was diagnosed with lower lobe pneumonia of the right lung. The results of the laboratory tests were presented below in Table 1.

A thoracic ultrasonography (USG) showed trace amount of pleural fluid in the right lower region. He was diagnosed with community acquired pneumonia and put on intravenous fluids and oxygen at a rate of 6 L/min. Prompt treatment of ceftriaxone 100 mg/kg/day, clarithromycin 15

**Adres / *Correspondence* :** Nazile Ertürk
Mugla Sitki Kocman University Research and Training Hospital, Department of Pediatric Surgery, Mugla,Turkey
**e-posta / *e-mail* :** erturknazile@mu.edu.tr

mg/kg/day, and vancomycin 40 mg/kg/day was started.

**Table 1.** Blood test results.

| Parameters | Results |
|---|---|
| WBC | $31.2x10^3$ $mm^3$ |
| Hgb | 10.3 g/dL |
| CRP | 414 mg/L |
| Peripheral smear | %90 neutrophils |
| ESR | 104 mm/hour |

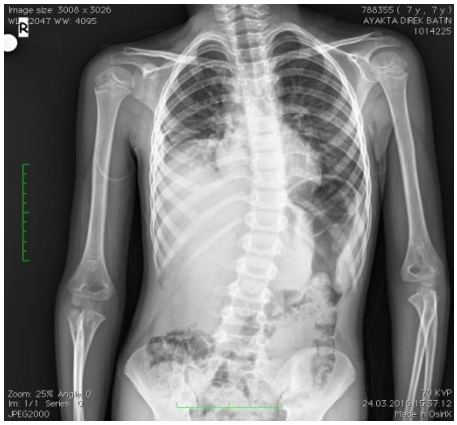

**Figure 1.** The admission chest X-Ray shows pneumonic infiltration and scoliosis of the thoracoabdominal vertebrae.

The patient's abdominal pain was completely resolved at the third day of treatment, and his body temperature decrease to 37.5°C. At the fifth day, however, he developed fever, increased restlessness, and diminished breath sounds over the middle and lower lobes of the right lung, which prompted a repeat CX-R (Figure 2) that revealed an opacity covering entire right hemithorax. Therefore, a repeat thoracic USG was performed, which showed an increased amount of fluid containing fibrotic septa and bands suggesting a complicated pleural effusion in the right pleural space. The work up for possible tuberculosis suspicion eventuated in negative PPD test.

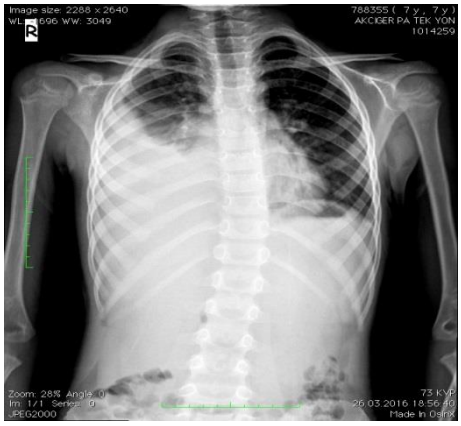

**Figure 2.** Chest X-Ray shows marked pleural fluid in right hemithorax. Ultrasonography showed loculations. A decision was made for chest tube insertion.

A chest tube was placed to the right pleural space, and approximately 200 cc purulent pleural fluid was drained. The pleural fluid analysis demonstrated that the density of fluid was 1020, pH was 7.5 (compatible with transudate), LDH level was 2860 U/L (compatible with empyema), glucose level was 9.3 mg/dl (compatible with empyema), and albumin level was 2.43 g/dl. Simultaneous serum LDH level was 315 U/L, glucose level was 182 mg/dl, and albumin level was 3.14. The pleural fluid/serum LDH ratio was 9 (compatible with empyema). The Gram staining of the pleural fluid revealed squamous epithelial cells, Gram positive cocci, and 5-6 PNL cells in every zone. No bacterial proliferation occurred in bacterial cultures. Based on these findings, empyema was considered as the most probable diagnosis. A chest X-Ray was obtained one day after chest tube insertion (Figure 3) and thoracic ultrasonography showed the persistence of loculations. Therefore, intrapleural fibrinolytic administration was considered, and 5 mg tPA (Metalyse 1000 U; Tenectelase, Boehringer Ingelheim//Germany) diluted in 40 ml isotonic saline was administered through the chest tube for three days. Then, chest tube was clamped and re-opened 1 hour later. The patient was also started on 2000 calorie/day enteral formula for energy support.

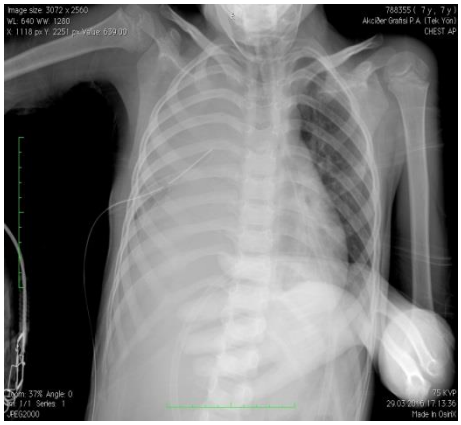

**Figure 3.** Chest X-Ray obtained after chest tube insertion. It is evident that the drainage is not sufficient.

On the 10th day of the therapy, ceftriaxone treatment was stopped and ceftazidime was started due to insufficient clinical improvement, high level of serum C-reactive protein (CRP) (170 mg/L), and severe increase of WBC count in hemogram (32.4 x103 mm3). Three days after ceftazidime treatment peripheral leukocytosis regressed (17.16x103 mm3) and CRP level decreased (35.77 mg/L). Chest tube was removed. Vancomycin and clarithromycin treatments were stopped at the 15th day of therapy, however, ceftazidime treatment pursued in order to complete a 10-day treatment interval. The final control serum CRP level was 26 mg/L, WBC count was 13.6x103 mm3, and Hgb was 9.3 g/dL.

On the 20th day of therapy a repeat CX-R (Figure 4) revealed significant resolution of pleural fluid. When he was found to have all his clinical and laboratory signs normalized, discharged to re-

admit within two weeks, a control chest X-Ray (Figure 5) showed resolved radiological signs despite the persistence of some residual fluid.

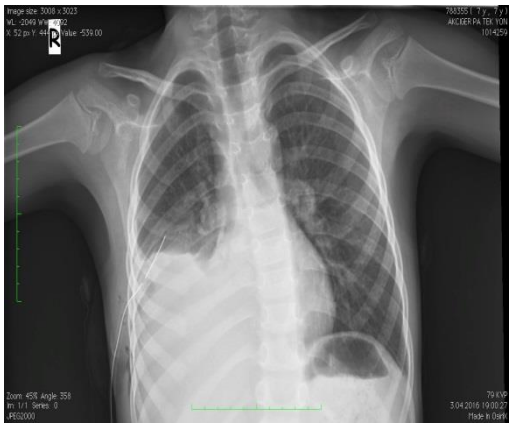

**Figure 4.** Chest X-Ray after a three-day course of fibrinolytic therapy.

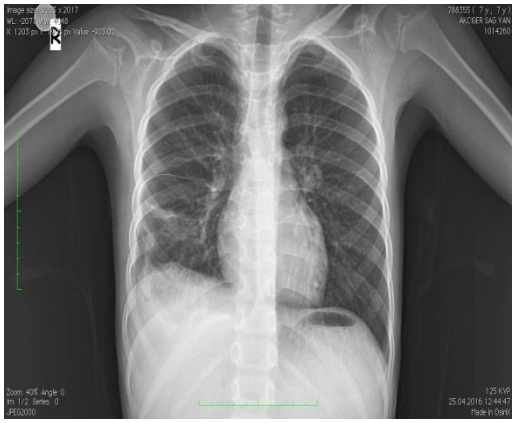

**Figure 5.** Chest X-Ray obtained 10 days after discharge.

## Discussion

The term pleural effusion refers to fluid accumulation in the pleural space due to excessive fluid production, reduced absorption, or both (2). It is most frequently of infectious (mostly bacterial) origin in the childhood period. The ones of viral origin are usually asymptomatic and characterized by spontaneous resolution (3). Streptococcus pneumoniae is the most common etiologic agent of paraneumonic effusion and empyema. Other agents include Haemophilus influenza type B, and in developing countries, staphylococci and mycobacterium tuberculosis (4). The diagnosis of the condition is made by physical examination and chest X-Ray. Thoracic USG, when performed by skilled operators, is superior to upright and supine chest X-Ray in detecting pleural effusion. It may distinguish effusions that have a solid or fluid character; it may also show free floating or loculated fluid; and it may give an idea for the level of thoracentesis (5). Computed tomography (CT) of the lung may be useful in defining fluid localization, accompanying emphysema, and pneumonia. However, it was reported that routine use of lung CT has minimal benefit for selecting appropriate initial therapy (6). Pleural effusion may be exudate or empyema in character. To identify its character, thoracentesis is indicated. Pleural biopsy or flexible bronchoscopy may be used in the presence of treatment unresponsiveness, unexplained fluid, or a high index of suspicion for a malignancy.

In effusions with transudate characteristics, the treatment primarily consists of the underlying condition. In case of empyema, on the other hand, fluid drainage, sterilization, lung re-expansion, and functional normalization are aimed (7). An antibiotherapy first aims to cover community acquired microbial agents based on a child's age, and the treatment is then tailored by culture results.

Effusions that progress or that cause respiratory compromise are managed by chest tube insertion (7). Other indications include a blurry thoracentesis fluid, a positive gram positive staining of a fluid sample, any proliferation of bacteria in fluid cultures, or pH<7, glucose <40 mg/dL, or LDH >1000 IU in the biochemical analysis of the fluid. The duration of chest tube removal is mainly determined by the patient's clinical status, and other removal criteria include daily fluid discharge of <10-15 ml, clearing of fluid discharge, and a decrease in acute phase reactants (7).

Chest tube may become ineffective when an effusion becomes fibropurulent in character or it contains loculations. In such situations, fibrinolytics are administered into pleural space, aiming the resolution of fibrin strands and opening lymphatic pores. Agents used for this purpose are streptokinase, urokinase, and tissue plasminogen activator (tPA). Studies have shown that fibrinolytics are successful in 80% to 90% of cases. St Peter et al. compared decortication via video-assisted thoracoscopic surgery (VATS) and tPA administration through chest tube in a prospective randomized trial. They found no significant differences between the two groups in terms of duration of hospital stay, number of days requiring oxygen therapy, time to resolution of fever, and need for analgesics (8).

Fibrinolytic agents usually cause mild adverse effects. Restlessness during intrapleural injection, temporary staining of pleural fluid with blood, fever, and rarely massive bleeding can occur (7).

In conclusion, in children with parapneumonic pleural effusion and empyema, intrapleural fibrinolytic administration in conjunction with chest tube insertion should be considered as an alternative to surgery due to its less invasive nature.

**Informed Consent:** Written informed consent was obtained from patient who participated in this case (17.11.2016).

## References

1. Chonmaitree T, Powell KR. Parapneumonic pleural effusion and empyema in children. Review of a 19-year experience, 1962-1980. Clin Pediatr (Phila). 1983;22(6):414-9.
2. Diaz-Guzman E, Dweik RA. Diagnosis and management of pleural effusions: a practical approach. Compr Ther. 2007;33(4):237-46.
3. Givan DC, Eigen H. Common pleural effusions in children. Clin Chest Med. 1998;19(2):363-71.
4. Freij BJ, Kusmiesz H, Nelson JD, McCracken GH Jr. Parapneumonic effusions and empyema in hospitalized children: a retrospective review of 227 cases. Pediatr Infect Dis. 1984;3(6):578-91.
5. Kelbel C, Borner N, Schadmand S, et al. Diagnosis of pleural effusions and atelectases: sonography and radiology compared. Rofo. 1991;154(2):159-63.
6. Jaffe A, Calder AD, Owens CM, Stanojevic S, Sonnappa S. Role of routine computed tomography in paediatric pleural empyema. Thorax. 2008;63(10):897-902.
7. Balfour-Lynn IM, Abrahamson E, Cohen G, et al. BTS guidelines for the management of pleural infection in children. Thorax. 2005;60 Suppl 1:11-21.
8. St Peter SD, Tsao K, Spilde TL, et al. Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. J Pediatr Surg. 2009;44(1):106-11.