CASE REPORT

The first use of combination of Intrapleural Fibrinolytics (Alteplase & DNAse) for pleural infection in Malaysia

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SUMMARY

The use of a combination of intrapleural fibrinolytics or tissue plasminogen activator(tPA) Alteplase and deoxyribonuclease (Dnase) has been increasing for cases of complicated pleural infection/parapneumonic effusion worldwide. Its efficacy and success rate in selected cases of complicated parapneumonic effusion unresponsive to antibiotics and chest drainage are well documented. This case report demonstrates the first use of combination intrapleural fibrinolytic (Alteplase) and DNAse (Pulmozyme) in Malaysia for a case of pleural infection/parapneumonic effusion.

INTRODUCTION

Pleural infection or Parapneumonic effusion (PPE; i.e., pleural fluid that results from pneumonia or lung abscess) is the most common cause of an exudative pleural effusion. PPE may be the consequence of either community-acquired or nosocomial pneumonia. A complicated parapneumonic effusion is a parapneumonic pleural effusion for which an invasive procedure, such as tube thoracostomy, is necessary for its resolution, or a parapneumonic effusion in which the bacterial cultures are positive. Early antibiotic treatment and effective pleural drainage usually prevents the development of PPE and its progression to a complicated PPE and empyema. Intrapleural instillation of fibrinolytics is an option if the infected pleural fluid is loculated, septated and is resistant to conventional chest tube drainage. The use of combination of intrapleural fibrinolytics or tissue plasminogen activator (tPA) Alteplase and deoxyribonuclease (Dnase) for cases of complicated pleural infection/PPE is becoming more common worldwide. Its efficacy and success rate in selected cases of complicated parapneumonic effusion which do not respond to antibiotics and chest drainage are well documented, but it has not been reported in Malaysia.

CASE REPORT

A 44-year-old Chinese male, smoker presented to our hospital with symptoms of fever, severe right sided pleuritic pain and increasing shortness of breath for one week prior to admission.

Vital signs revealed blood pressure 148/76mmHg, pulse rate 95 beats/min, oximetry 97% and temperature of 38°C. Clinical examination revealed that air entry was reduced over the right lung base and stony dullness noted on percussion.

Initial baseline blood investigations revealed raised Total White Cell count 18.0 x10/µl, and a raised CRP level at 158mg/L. Chest x-ray showed a small right sided pleural effusion which was confirmed with a subsequent CT thorax which showed a pleural effusion with compressive atelectasis of the right lower lobe. There was no evidence of pleural abnormality or 'split sign' to suggest empyema thoracis at that particular time

In view of the above clinical picture, a diagnosis of parapneumonic effusion was suspected and the decision for chest tube insertion for drainage was made by the on-call physician. The patient was referred to the thoracic surgeon for chest tube drainage insertion. A size 28 Fr chest drain was inserted under local anaesthesia and 700cc of slightly turbid pleural fluid was removed with improvement of symptoms, and the tube was connected to a underwater seal bottle. He was started on intravenous Ceftriaxone and Azithromycin with regular analgesics given. The pleural fluid analysis revealed pH 7.25, protein 30g/L, RBC count 1000/µL, and neutrophils predominance (34%). There was no organism detected on Gram stain, no growth obtained from Pleural Fluid Culture and AFB the smears were negative.

Serial chest x-rays were done for the next 48 hours (Figure 1) which showed persistent opacity with minimal chest drainage subsequently. The case was then referred to the Respiratory Consultant on 3rd day of admission for further management. The persistent opacity on the chest radiograph was evaluated with bedside ultrasonography of thorax which revealed early loculations and septations of the pleural fluid. The drain was fluctuating minimally since tube insertion despite good positioning. The patient was still short of breath, still febrile(38 degrees) and blood parameters showed persistently raised CRP levels at 143 mg/L.

He was then treated as non-resolving complicated parapneumonic effusion. Antibiotic therapy was escalated to intravenous Cefoperazone-Sulbactam for broader spectrum coverage and patient was offered intrapleural instillation of fibrinolytics (Alteplase®) with DNAse (Pulmozyme®) for three doses for effective removal of the infected pleural fluid via the chest drain. He was also offered the option of surgical drainage and decortication via Video Assisted Thoracoscopic Surgery (VATS) but declined.

This article was accepted: 14 November 2018
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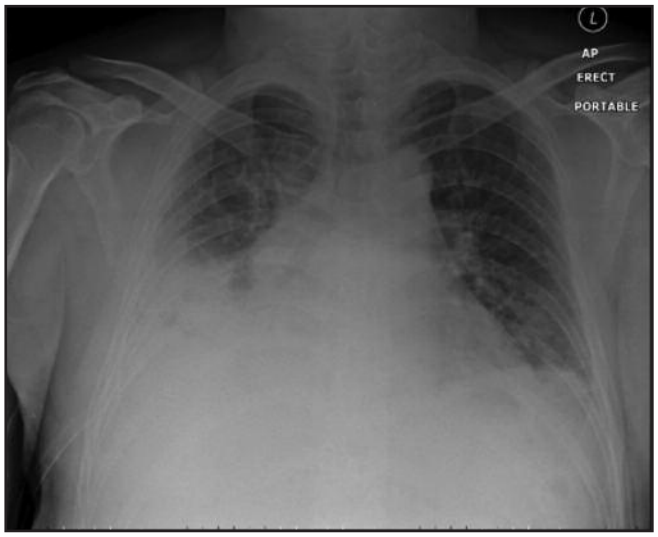

Fig. 1: Chest Radiograph after one day of tube thoracostomy showing persistent opacity likely to represent complicated parapneumonic effusion.

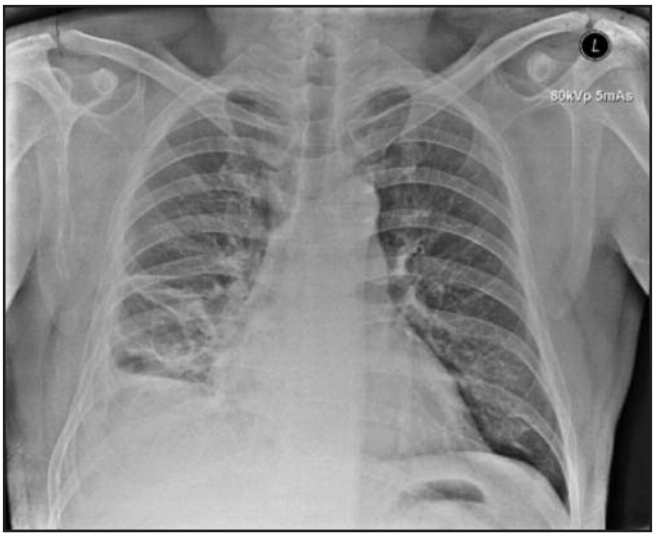

Fig. 2: Chest Radiograph done 24 hours after completing the intrapleural instillation therapy showing partial resolution of parapneumonic effusion.

Instillation of intrapleural Alteplase 16mg (in 50mls normal saline) followed by Pulmozyme 2.5mg (DNAse) (in 50mls normal saline) was given sequentially in three doses (12 hours apart) under sterile and aseptic technique.

Throughout the above instillation period, monitoring with drainage charting of pleural fluid output, the nature of pleural fluid evacuated (serous or bloody pleural fluid), temperature charted, and patient pain score was done every 6 hours. Investigation done were: daily chest radiograph, daily bedside ultrasonography of the thorax and CRP levels. After 24 hours of the above instillation, there was clinical improvement in terms of lower pain and dyspnoea scores, patient being afebrile and good drainage of the infected pleural fluid. The total drainage of the evacuated infected effusion post instillation was 1200cc (serous).

Serial chest x-rays showed that the amount of effusion was decreasing and CRP levels reduced to 109mg/L (Figure 2) after 24 hours post instillation. Daily bedside ultrasonography showed residual pleural thickening with no effusion left after the last dose of the above instillation.

The patient responded well to the above therapy with chest drain removed on day-6 of admission and he was discharged with continuation of oral antibiotics for another one week.

On follow up review at clinic at period of two weeks, one month and two months post discharge revealed that he was well, asymptomatic and chest x-ray showed only residual right sided lower zone pleural thickening which is seen commonly in resolved recent pleural infection.

DISCUSSION

Complicated parapneumonic effusion or pleural infection is common and is associated with high morbidity if therapy is inadequate. The usual therapy for complicated parapneumonic effusion or empyema involves broad spectrum antibiotics and drainage of infected pleural fluid by tube thoracostomy.[1,2] Antibiotic therapy used should be broad spectrum and effective against anaerobic organism as well. Choices of management commonly employed where community acquired organisms are involved are aminopenicillin with B-lactamase inhibitor (co-amoxiclav) or metronidazole, clindamycin alone or in combination with ciprofloxacin or a cephalosporin. Alternative agents include carbapenems, third generation cephalosporins or broad spectrum antipseudomonal penicillins such as piperacillin.[1,2]

Prompt evacuation and effective drainage of the infected fluid is the cornerstone of the management.[1,2] In complicated cases, inability for adequate evacuation of the infected fluid is usually due to dense septations and loculations which was seen in this case, and this may necessitate surgical drainage in up to 20-30% of patient.[3] Various intrapleural fibrinolytic agents have been used to improve the drainage albeit with mixed results.[4] The most promising therapy thus far is the combination of intrapleural tpa(Alteplase) and DNAse (Pulmozyme) which have been shown to improve the drainage of infected effusion thus reducing the need for surgical intervention and length of hospital stay.[4] Its use has been increasing worldwide for cases of complicated parapneumonic effusion in adults which does not respond to chest drainage and antibiotics.[4]

The above case is the first reported use of combination of intrapleural Alteplase (tPA) together with DNAse (Pulmozyme) for a case of complicated pleural infection in Malaysia. There are reported cases in Malaysia of single agent intrapleural fibrinolytics (Alteplase only) use in the management of parapneumonic effusion with some success.[5]

The combination of Alteplase (for lysis of adhesions) and DNAse (to reduce pus/infected fluid viscosity) has been shown to improve outcomes.[2,4] In a largest multicentre case series,

patient receiving combinations of tPA/DNAse responded well in terms of radiographic clearance, fluid evacuation, CRP levels reduction and clinical improvement; thus avoiding surgical intervention(2). This is recognised as an effective and safe treatment and has been touted as a 'rescue therapy' with a "minimally invasive' approach as it only usually requires a small bore drain (chest drain <16F in most cases) in selected patients who do not respond to antibiotics and tube thoracostomy drainage alone.[2]

The optimum dosage, protocol and duration of therapy of the above intrapleural instillations in pleural infection still remains undefined (usually less than total of six doses) but the dose opted in this case was adopted from the largest multicentre series.[2] In terms of adverse events and complications, the most common one was pain requiring analgesia escalation (19.6%) and haemothorax (1.8%).[2]

However, a few questions remain unanswered in this combination therapy. such as its cost effectiveness and its direct comparison versus surgical drainage (VATS) and this is still being debated. The other obstacle for the use of this combination intrapleural therapy specifically in Malaysia is the difficulty of obtaining the DNAse (Pulmozyme) component in Malaysia as it is licensed only for use in cystic fibrosis and it is only commonly available outside of Asia Pacific region.5 The combination use of the above therapy also is considered "off label" by FDA and is not yet licensed for use in pleural infection.

In conclusion, the majority of cases of pleural infection/complicated PPE will respond to broad spectrum antibiotics and effective tube thoracostomy drainage. However, in selected cases, when the chest drainage is impaired and clinical improvement is lacking and especially if patient is a poor surgical candidate, then the use of combination intrapleural tPA/DNAse should be strongly considered as an alternative to surgical intervention.

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