A Successful Intra-Pleural Fibrinolytic Therapy With Alteplase in A Patient with Empyematous Multiloculated Chylothorax

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ABSTRACT
Chylothorax is a collection of chyle in the pleural cavity resulting from leakage of lymphatic vessels, usually from the thoracic duct. In majority of cases, chylothorax is a bacteriostatic pleural effusion. Incidence of infected or even empyematous chylothorax are not common. Here, we report a case of a 57-year-old man with end stage renal disease and complete central venous stenosis who presented with recurrent right-sided chylothorax. It was complicated with sepsis and multilocated empyema and treated successfully with intra-pleural fibrinolytic therapy using alteplase.

Key Words: Chylothorax, empyema, intrapleural fibrinolysis

Introduction
Chyle is a non-inflammatory, bacteriostatic fluid with a variable protein, fat and a lymphocyte predominance of the total nucleated cells. (1,2) Incidence data are available for only post-operative chylothorax, which can occur after almost any surgical operation in the chest. It is most often observed after esophagectomy (about 3% of cases), or after heart surgery in children (up to about 6% of cases) (1). It is uncommon for chylothorax to be infected and loculated (2).

Chylothoraxis a condition that needs to be taken seriously; a patient who persistently loses chyle will be losing considerable amounts of fat and fat-soluble vitamins, proteins, electrolytes, immunoglobulins, and T-lymphocytes, with resulting malnutrition, weight loss, and an impaired immune system. (1) The management of chylothorax depends on the underlying cause and most of the cases were treated conservatively(1-2).

Empyematous chylothorax on the other hand should be treated more aggressively. Many of these patients will require antibiotics, thoracoscopic or open debridement and drainage.[3] Intra-pleural fibrinolytic therapy (IPFT) has been established as one of potentially beneficial treatment option for parapneumonic effusions and empyema in the adult population for the outcomes of treatment failure (surgical intervention or death) and surgical intervention alone (4). Our patient had chylothorax which was complicated with empyema and treated with combination of intravenous antibiotic and sequential intra-pleural alteplase (without deoxyribonuclease) administered to different pleural locules.

Case Report
Our patient is a 57-year-old man with end stage renal failure due to long standing hypertension; dyslipidaemia and ischaemic heart disease. He attended regular dialysis 3 times per week using right brachiocephalic (BCV) fistula. He had multiple admissions to hospital for thrombosed loop graft and veno-thromboplasty between 2011 to 2015. In early 2015, computed tomography (CT) scan of thorax showed complete occlusion of left brachiocephalic subclavian vein with well-established collaterals and severe stenosis (95%) of right BCV with multiple collaterals. But he remained asymptomatic during that period.

In November 2016, he was admitted to a district hospital due to progressive shortness of breath which turned out to be massive right-sided...
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Fig. 1. Chest radiograph showed massive right-sided pleural effusion

Fig. 2.a,b. CT scan thorax axial view (a) showed multiloculated right-sided pleural effusion with split pleural sign. CT Scan thorax coronal view (b) revealed a multiloculated pleural effusion with chest drain in-situ at the right lower lobe.

Chylothorax. He was referred to our center for further management. CT scan of thorax showed complete central venous stenosis with established collaterals. A subsequent CT lymphangiogram revealed termination of lipiodol opacification in the lymph nodes and lymphatic vessel at level of right third thoracic vertebrae (T3) and left 5th thoracic vertebrae (T5). Pigtail-catheter (8F) was inserted to drain the chylothorax and he was subsequently scheduled for lymphovenous bypass surgery in February 2017.

Unfortunately, he had recurrence of the chylothorax while waiting for surgery and during one of the admissions; he was discharged with pigtail catheter. Two weeks later, he presented with sepsis. He reported poor drainage from the pigtail catheter. Clinically, he was tachypnoeic with respiratory rate 30/min, heart rate was 110/min and febrile at 38 degrees with blood pressure of 85/50 mmHg. He had reduced breath sounds and stony dullness over the right lung. Chest radiograph showed massive right-sided pleural effusion (figure 1A). A bed side thoracic ultrasound showed multiseptated, multiloculated right pleural effusion. The blood investigations showed leukocytosis with total white cell count (TWCC) was $31 \times 10^9$ and C-reactive protein (CRP) was 26.54 mmol/L.

Pleural fluid was milky in colour. Biochemistry of the pleural fluid revealed LDH: 1147 mmol/L, and triglyceride of 9.6 mmol/L (849.5 mg/dL), with pH of 7.0. Pleural fluid bacterial culture, Mycobacterium Tuberculosis culture and AFB were negative.

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Patient was treated for empyema with intravenous tazobactam/piperacillin 4.5 gram twice daily; and intradialytic total parenteral nutrition was initiated. Despite regular flushing, the pleural catheter was not draining well. Another CT scan of thorax was performed, showed increasing size of right-sided pleural effusion which was loculated with pleural thickening suggestive of early sign of empyema (Figure 2A and 2B). A new rocket seldinger chest drain (12F) was inserted at the right lower thoracic area, however the drainage was still minimal (<50cc/day).

A multidisciplinary team consisting of pulmonologist, vascular surgeon, cardiothoracic surgeon, interventional radiologist, nephrologist, and dietician were involved in his care. Due to the underlying comorbidities and high risk of mortality with thoracotomy and decortication, we decided to instill intra-pleural fibrinolytic therapy using alteplase for the multiloculated pleural effusion with. Another chest drain was inserted at the upper right thoracic region. Sequential intrapleural alteplase was given to each chest drain.

A total of 20mg intrapleural alteplase given at right lower chest drain (5 mg 12 hourly) and 30mg alteplase (5 mg 12 hourly) at the upper right chest drain.

Patient made a remarkable improvement even after the first instillation of alteplase (figure 3A-B). A total of 2.5 L milkish-pink coloured effusion was drained collectively. After completing antibiotics, he was discharged well after 4 weeks of admission. Dietary restriction (fat free diet and medium-chain triglycerides) were emphasized. He did not develop any recurrence of chylothorax since then and surgery was cancelled. Chest radiograph before he was discharged showed minimal effusion with an area of non-expandable lung at the right apex (figure 3C). As he was asymptomatic, he was treated conservatively. He is doing well currently.

Discussion

Chylothorax refers to accumulation of chyle in the pleural space and is an infrequent, but potentially life-threatening complication, with profound respiratory, nutritional, and immunological consequences (5). It is characterized by elevated pleural fluid triglyceride level of more than 110 mg/dL (1.24mmol/L), lack of cholesterol crystals and the presence of chylomicrons which is a gold standard in diagnosing chyle pleural effusion (2). The causes of chylothorax can be divided as traumatic (iatrogenic and non-iatrogenic), non-traumatic (tumour e.g lymphoma, malignant or benign tumor), idiopathic (congenital) and other cause chylothorax (2).

As for our patient, CT lymphangiogram showed cessation of lipiodol opacification of lymph nodes and lymphatic vessel at level T3 on the right and T5 on the left consistent with central venous thrombosis due to multiple jugular catheter insertion in the past. The finding of central venous thrombosis is a known cause of the recurrent chylothorax. Due to multiple procedures involving pleura, he developed empyema. The management of our patient was complex in which we had to deal with chylothorax and empyema as two different entities. The empyema which was loculated; and him being high risk procedure for surgery makes the situation more complicated.

Treatment for chylothorax can be divided into treatment of underlying disease, conservative or surgically approach (1-2). After thoracentesis, patient can be treated conservatively with...
adequate fluid and electrolyte replacement along with appropriate nutrition (1). The idea of conservative treatment is to reduce the low of lymph to the thoracic duct to the point that the lymph leak will heal and the chylothorax eventually resolve (1-2). As in our patient, he was given intradialytic TPN to replenish the nutrition; and post discharge; he was advised for diet containing medium-chain triglycerides (MCT). MCT is absorbed directly into the portal venous system without going through the intestinal lymph vessels and the thoracic duct (1).

Surgical approach is indicated for failure or conservative treatment resulting recurrent chylothorax. Surgical option varies such as thoracic duct ligation, pleureperitoneal shunt, pleurectomy or lymphovenous bypass; depending on underlying disease and anatomy (1). Other option such as pleurodesis also had beneficial result to prevent chylothorax in situation where the lung is fully expanded (1). Other therapies such as octreotide-a somatostatin analogue that are thought to reduce flow rate of chyle production by inhibiting gastric, pancreatic, and biliary secretion-has been reported in several case reports but so far there was no randomized control trial (6).

An infected, loculated or even empyematous chylothorax is not common since the chyle effusion itself is bacteriostatic (2). However, it was reported by Lautin et al (7) of a patient with loculated mediastinal chylothorax following esophagogastrectomy. In our patient, the cause of infected chylothorax was likely lack of proper care over prolonged pleural drainage cathether at home, resulting ascending infection to the thoracic wall and intra-pleural space causing multiseptation and multiloculation.

We opted for intra-pleural alteplase alone for the treatment of empyematous chylothorax; as DNase is not licensed for intra-pleural use in our country. Contrary to MIST 2 trial which showed efficacy of combining alteplase with DNase, our patient responded with the use of alteplase alone (8). Similar case report was published before on the use of intra-pleural alteplase in empyema in selected cases (9).

In conclusion, a multiloculated empyematous chylothorax is rare, yet the management is generally similar with loculated parapneumonic effusion or empyema. In our patient, the combination of ultrasound guided pleural drainage, intra-pleural fibrinolytic agent, intravenous antibiotic, intra-dialytic TPN and diet containing medium-chain triglycerides (MCT), were the key factors for achieving a good outcome. Frequent thoracocentesis in chylothorax should be avoided since it may introduce infection resulting in empyema. Pleural infection carries high mortality. Although DNase are considered necessary to improve intrapleural fibrinolytic therapy; in our patient, the use of intrapleural alteplase alone produced good outcome especially when he is not a candidate for thoracotomy.

**Informed Consent:** Written informed consent was obtained from this patient for this publication.

**References**