Review Article

Updates on the pathophysiology and therapies of chylous pleural effusion: A narrative review

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ABSTRACT

Chylous pleural effusion (CPE) is a milky pleural fluid that contains high levels of proteins, cholesterol, triglycerides, or chylomicrons. The main cause of CPE is disruption of the thoracic duct caused by traumatic or non-traumatic causes. High triglyceride, cholesterol, and/or chylomicron levels confirm the diagnosis. Recognizing the chyle leak site and underlying etiology is critical to the management of this clinical condition. There is no specific consensus on chylothorax treatment. However, a multidisciplinary (medical, surgical, and oncological) team approach is recommended.

Key words: Chylous pleural effusion, Epidemiology of chylous effusion, Pathophysiology pf chylous pleural effusion, Management of chylous pleural effusion

The fundamental purpose of physiological pleural fluid is to maintain negative intrathoracic pressure, thereby ensuring the proper function of the lungs throughout the respiratory phases [1]. Pleural effusion (PE) can have various causes, including infections, inflammation, autoimmune diseases, hydrostatic and oncotic pressure disorders, drugs, iatrogenic factors, and malignancies. Therefore, examining the pleural fluid is important to find the underlying cause. The appearance of PE fluid can vary depending on the underlying condition [2].

PE is often categorized into two main types, transudative or exudative, based on the relative amounts of lactate dehydrogenase and protein in the pleural fluid compared to the serum [1]. The categorization is derived from Light's criteria, a set of guidelines that aid in recognizing the specific illness process [3]. Differentiations between the fluid macroscopic features may also be conducted by a preliminary examination of their color and consistency. The visual characteristics of the fluid may range from being transparent and clear to being turbid and purulent or even hemorrhagic, resulting in a reddish PE. In certain cases, the fluid may appear bilious or milky, as is the case with chylous PE (CPE) [2,4]. This comprehensive and non-systematic review study aims to provide physicians with valuable insights into the pathophysiology, epidemiology, etiology, and possible available therapies of CPE to assist physicians in the effective treatment of this type of PE. To achieve this aim, we searched for published articles in Google Scholar, PubMed, and Google using texts and phrases, such as PE pathophysiology, CPE, mechanisms of CPE, thorax duct obstruction causes, treatments of CPE, CPE therapies updates, and CPE outcomes. We limited the search period to the past 4 years (i.e., between August 2019 and August 2023).

CPE

CPE, also called chylothorax, is due to the buildup of chylous fluid between the pleural layers. Two types of high lipid-level PEs are commonly encountered: Chylothorax and cholesterol PE [5].

CHYLOUS FORMATION AND TRANSPORT

Chyle is formed in the small intestine and consists of lipids, proteins, electrolytes, and T lymphocytes [6]. Dietary consumption of triglycerides (TGs) is essential for humans to synthesize chyle. TGs can be classified into small, medium, or long chain TGs,

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which are determined by the length of the fatty acid molecules. Through the hydrolysis of TG by intestinal lipases, small and medium chain TGs are converted into free fatty acids, which are absorbed and passed into the portal circulation. The process of chylomicron formation occurs in the enterocytes of the jejunum, where long-chain TGs interact with phospholipids, cholesterol, and cholesterol esters to produce chylomicrons, which are absorbed by the lacteals (the tiny lymphatic vessels inside the villi) that delimit the villi's epithelial layer small intestine. The lacteals merge to create larger lymphatic vessels, which merge into the circulation through the thoracic duct (TD) and the left subclavian vein [7].

The human small intestine possesses a highly intricate transportation system, with the intestines playing a pivotal role in conveying approximately 2.4 L of chyle to the systemic circulation daily. However, damage, rupture, or dysfunction of TD may result in chylothorax [8,9]. TD anatomy course variation is significant, and the damage extent determines the site of CPE occurrence rate, which is either unilateral or bilateral PE [6]. In the majority of cases (78%), chylothoraxes are unilateral, with the right-side predominating (67%), while 33% involve the left hemithorax [6,8,9].

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF CPE

CPE is rare, accounting for 3% of all PE cases [10]. The frequency of CPE ranges from 0.52% to 11.7% in different nations [11]. Traumatic causes account for more cases than non-traumatic causes. Iatrogenic TD damage during chest operations [12], especially esophageal resections (4%), is the most common cause of trauma-related cases because the TD is located close to the esophagus and does not have a straight path [12].

CPE is a rare but well-known clinical entity that can occur as a complication of thoracic and esophageal surgeries, heart failure, tense ascites, or hematologic malignancies. It shows no gender or age preference. The prevalence of CPE after various cardiothoracic surgeries is between 0.2% and 1%. Although the morbidity and mortality rate of this disease is approximately 10%, early diagnosis and prompt treatment can significantly improve the outcome [13].

In this type of PE, the pathophysiology is due to the disruption of pleural lymphatic drainage, which results in increased intra-lymphatic vessel pressure [13], leading to the accumulation of chyle in the pleural space. Chyle fluid is characterized by its milky appearance, whitish color, and opalescent nature. However, it may present with inconstant fluid color and chemical features. Non-milky appearance is not rare [14].

Another mechanism of CPE is that the anatomical trajectory of the TD has a complicated nature, characterized by notable variability. Consequently, the chylothorax occurrence is contingent on the specific location and extent of the defect in the TD [7]. The convergence of the lymphatic channels results in TD formation, serving as a chyle transportation conduit and facilitating drainage to the left subclavian vein. A chyle effusion may be attributed to any damage inflicted on the main duct or one primary tributary as it traverses the thorax region [15]. It was reported that the chylothorax is a PE brought on by extravasation of the chyle in the intrapleural space due to TD blockage or injury. The chyle leak may sometimes be infra-diaphragmatic from the abdominal cavity [15].

The formation of pleural CPE in malignancy is primarily caused by compression or invasion of the TD and lymphatic obliteration due to tumor radiation therapy [16,17]. Non-traumatic CPE development mechanisms are multiple, which can be single or in combination. The mechanisms include direct cancerous damage or invasion of the TD, the transdiaphragmatic flow of chylous ascites to the pleural space, higher hydrostatic pressure draining chylous fluid in the pleura, and hyperpermeability of the lymphatic system [10].

Furthermore, main lymphatic drainage system disorders and malignancy can cause chyle leaks in the retroperitoneum, leaking to the pleura, causing CPE. The lower intrathoracic pressure compared to increased intra-abdominal pressure in tense ascites is the possible mechanism of fluid upstream from the abdominal cavity to the pleura space through small transdiaphragmatic holes or ducts. Another possible mechanism is that in tense ascites, as in liver cirrhosis or malignant ascites, the intra-abdominal pressure will be higher, compromising the drainage functionality of the TD [9].

In heart failure, it was thought that due to increased superior vena cave hydrostatic pressure, the capillary filtration rate raises venous pressure, which is reflected in the TD, leading to an increase in TD blood and lymphatic flow to about 12 times than the usual rate. However, the neck's venolymphatic junction stiffness slows lymphatic flow [7]. Moreover, the collaterals of the lymphatic venous formation increase when the left subclavian vein hydrostatic pressure increases, slowing down lymphatic draining. Although the concept of collateral formation is to reduce the pressure in those junctions, they are usually unable to handle the increased flow of lymph, which could cause chyle to leak into the abdominal or pleural space [18].

CPE CLINICAL PRESENTATION AND DIAGNOSIS

Chylothorax symptoms depend on the CPE volume. Asymptomatic small chylothorax is sometimes detected incidentally, whereas large chylothorax can cause mechanical compression, leading to breathlessness, reduced exercise capacity, and chest pressure. Increased body temperature and chest pain are usually absent. However, patients can tolerate substantial amounts of chylothorax if it accumulates gradually and the respiratory system adapts. Post-traumatic CPE can occur 10 days following the injury; hence, it must be kept in mind in diagnosing the cause of CPE. In surgical patients, chylothorax may be detected as the PE fluid persistent to drain from chest tubes.

Depending on fluid size and location, dullness or stony dullness, percussion, and reduced breath sounds may be noted in physical examination. Chylothorax cases are typically unilateral

in 80% of patients. Since the TD is located on the right side, it is more commonly affected than the left (in 60% of all cases). The final diagnosis of CPE relies on the direct study of fluid by measuring the TG level and lipid electrophoretic pattern (specifically chylomicrons). The most common criterion for determining the existence of chyle is a TG level of >110 mg/dL or chylomicrons existence in the PE fluid [19]. However, high chylomicrons or TG levels in the PE fluid do not rule out other factors that might contribute to pleural fluid production. The importance of CPE identification influences the therapeutic decisions for PE.

Non-traumatic CPE is characterized by a slow buildup of chyle inside the pleural space, occurring without any acute injury to the TD. Non-traumatic CPE is linked to various medical conditions, with malignancy being the cause in around 75% of instances. The origin of idiopathic chylothorax remains unexplained in a proportion of cases, estimated to be up to 9%. The appearance characteristics of pleural fluid do not possess sufficient sensitivity or specificity for diagnosing CPE. Hence, it is necessary to do biochemical testing for the pleural fluid. According to cholesterol, TG, and chylomicron levels in the CPE, the CPE was classified into three types of CPE (cholesterol, TG, and chylomicron CPEs). A diagnosis of CPE may be made when the pleural fluid TG level > 1.24 mmol/L (110 mg/dl) and the cholesterol level are <5.18 mmol/L (200 mg/dl). Lipoprotein electrophoresis may be required as a diagnostic tool to validate the diagnosis by identifying the existence of chylomicrons in the PE fluid, particularly when the diagnosis is uncertain. In contrast, cholesterol PE usually occurs due to prolonged pleurisy with high cholesterol levels [7]. However, this concept has been questioned. A cholesterol PE is usually diagnosed by radiographic scans showing thickened visceral and parietal pleural membranes, leading to lung entrapment. Most cases of cholesterol PEs are caused by rheumatoid or tuberculosis pleurisy [5].

It is believed that CPEs caused solely by TD leaks often have low lactate dehydrogenase (LDH) levels due to the lack of inflammation. They primarily comprise lymphocyte-produced exudates that are inconsistent in terms of protein. Thus, PEs that do not fit these criteria but exhibit TG concentrations exceeding 110 mg/dL or are positive for chylomicrons should be associated with other diagnoses contributing to PE formation. There are different available schemes for investigating malignant PEs. The types and diagnostic approach schemes of PE are summarized in Fig. 1.

ETIOLOGY OF CPE

The most common pathology of non-traumatic CPE is cancer, accounting for almost 33% of CPE. Lymphoma causes 75% of aggressive chylothorax, with non-Hodgkin lymphoma being the prevalent cause [5,9,20]. Metastatic epithelial tumors also cause CPE, although rarely. The remaining non-traumatic CPE causes account for only 20% [5]. Primary lymphatic diseases, like lymphangiectasia, may cause, although it is a rare disease. Lymphangioleiomyomatosis, due to abnormal smooth muscle cell growth, usually affects women. Up to 40% of lymphangioleiomyomatosis patients may get chylothorax at some point in their disease course [5]. Yellow nail syndrome can cause chylothorax, but the fluid is often non-chylous. This syndrome also causes nails to grow slowly and become brittle, predisposing to lymphedema, especially in the legs [5,21]. Diseases such as chronic liver cirrhosis, heart failure, and nephrotic disease usually cause transudative EFS, although they may cause CPE [5,14,22]. Box 1 contains the major causes of CPE.

TREATMENT OF CPE

The current treatment depends on the root cause and the specific clinical context. Non-operative alternatives include observing the condition, resolving the root cause of the disease, and locating the leak site [7]. Specific X-ray tests that focus on the lymphatic system can play an important role.

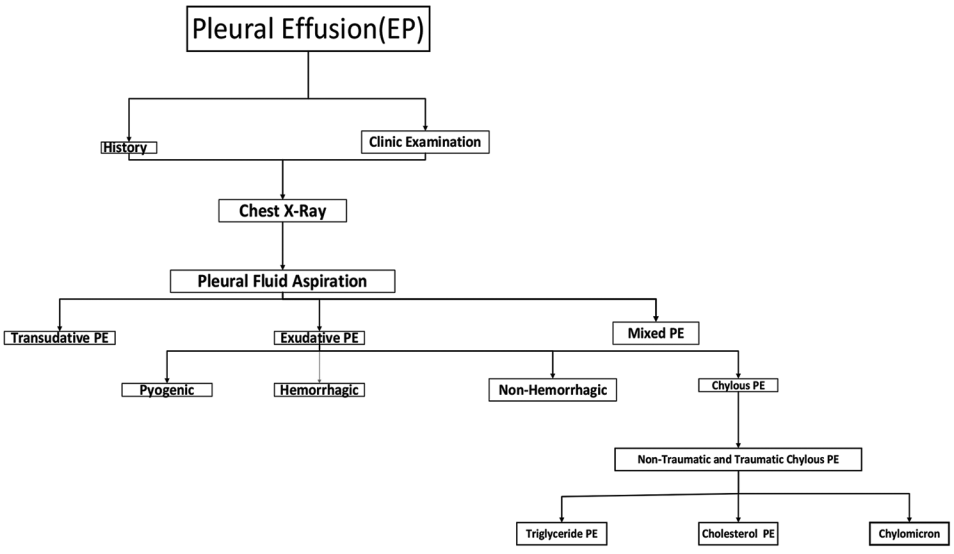

Figure 1: Types of pleural effusions and diagnosis scheme

Box 1: Causes of chylous pleural effusion
Cancer
Lymphoma (non-Hodgkins type)
Metastatic epithelial tumors
Primary lymphatic diseases (lymphangiectasia)
Lymphangioleiomyomatosis
Yellow nail syndrome
Chronic liver cirrhosis
Nephrotic syndrome
Heart failure
Ataxic telangiectasis

There is a need for further evidence regarding the optimal strategy for treating non-traumatic CPEs, with treatment strategies often dependent on the underlying etiology. Initial conservative treatment is often pursued as a preliminary approach, often within a certain period of time, before more invasive procedures are considered. The observational therapeutic strategies include implementing dietary adjustments such as adhering to a rigorous medium-chain TG diet or resorting to whole parenteral nourishment and intermittent thoracocentesis. The interventional surgical approach for managing this condition encompasses many procedures, such as pleurectomy, pleuroperitoneal shunting, chemical pleurodesis, thoracoscopic or thoracotomy-based repair or closure of the TD leaks, and TD embolization [22].

Furthermore, midodrine, sirolimus, and somatostatin/octreotide have been used to stop chyle production. TD embolization and pleurovenous or pleuroperitoneal shunting are two surgical options that have been successfully employed. A phased treatment plan, starting with less invasive options and progressing to more invasive ones, is the most beneficial for most patients [23-26]. Diet modification in CPE is an important maneuver, alleviating the symptoms, and reducing the recurrence rate following lymph node and pulmonary resection, as reported by Takuwa *et al.* [27]. It is advisable to use a multidisciplinary strategy, fostering effective collaboration among professionals in respiratory medicine, thorax surgery, oncology, interventional radiology, and dieticians. Decortication is the advised primary therapy option in cholesterol CPE, especially in symptomatic restrictive lung disease lung development as a complication [5]. The available therapies for CPE are listed in Box 2.

Box 2: Therapy of chylous pleural effusion
Observational therapy diet modification
Reducing chylous pleural effusion production (Midodrine, sirolimus, and somatostatin/octreotide)
Intermittent thoracentesis
Thoracostomy with chemical pleurodesis
Thorax duct embolization
Pleurectomy
Chemical pleurodesis (with Assistant thoracoscopy surgery)
Thoracoscopic or thoracotomy-based repair or closure of the thoracic duct
Pleuroperitoneal shunting
Pleurovenous shunting

DIETARY TREATMENT

Reducing or removing dietary long-chain fatty acids effectively minimizes chyle outflow and spontaneously closes leaks. Long-chain fatty acids are the building blocks of CPE fluid; limiting fat intake to <5 kcal per meal can lead to successful results [23]. Although this method may cause long-term fat shortage and malnutrition, venous fat hemorrhage may help address some drawbacks [28]. A balanced diet can be followed to obtain small- and medium-chain fatty acids, while long-chain fatty acids can be administered intravenously [29].

THORACENTESIS

Dealing with non-traumatic and non-surgical traumatic CPEs can be difficult and require immediate attention. To help ease the discomfort caused by pleural fluid, healthcare professionals often use intermittent therapeutic thoracentesis or an indwelling catheter for home drainage [30,31]. This method can be effective if the patient's pleural fluid decreases gradually. In cases of postsurgical CPE, a chest tube insertion is mostly necessary. However, it is important to remember that long-term pleural fluid drainage increases infection rate, severe malnutrition, and immunoglobulin depletion. Therefore, it is recommended that continuous PE fluid drainage should last for up to 2 weeks. Surgery may be necessary if the daily PE fluid drainage exceeds 1.5 L. It is essential to prioritize the patient's well-being and needs [26].

PLEURODESIS

Recurred fluid buildup can be frustrating despite making dietary changes and undergoing thoracentesis multiple times. However, there is no need to lose hope. Installing a chest tube drainage during video-assisted thorax surgery with talc power insufflation leads to successful pleurodesis in up to 80% of chylothorax cases, providing patients with much-needed relief. Moreover, TD ligation is conducted during surgical pleurodesis, which has an excellent success rate in preventing the development of new CPEs [32,33]. This invasive method is only used when pleurodesis and dietary modification have yet to be successful. Although TD ligation can cause lymphedema, it usually goes away after a few months due to the improvement of collateral lymphatic venous circulation connections [34].

EMBOLIZATION OF THE THORAX DUCT

The use of the cisterna chyli and significant retroperitoneal lymphatic ducts has become more common in treating traumatic and non-traumatic chylothorax. This includes percutaneous catheterization and embolization, where the TD is disrupted using a needle. The first step is to perform a transabdominal percutaneous needle cannulation, followed by a fluoroscopic

examination of the major retroperitoneal lymphatics and the first pedal lymph angiogram. Once the cisterna chyli is cannulated, the catheter is advanced, and contrast is implanted into the TD to locate the leak. Finally, coils and surgical hints are used to embolize the affected thorax section [35].

UPDATES ON CPE THERAPY

Somatostatin and octreotide have been proven to effectively reduce biliary, pancreatic, and gastric secretions and the overall amount of stomach lymphatic flow [36]. Due to the decreased chyle production and flow rates caused by these drugs, they can even repair the leak in TD independently [36]. As a result, this procedure has been known to benefit many spontaneous, congenital, post-operative, and cancerous instances. Although the ideal dosage and course of therapy are still being studied, the potential benefits of this treatment must be considered. Sirolimus, which is used to treat lymphangiomyomatosis, has also been found to reduce the likelihood of chylothorax in these patients. Hence, further novel studies are mandatory to assess the effectiveness of these drugs [37].

The pleural or pleuroperitoneal venous shunt is another effective method of resolving chylothorax by redirecting chylous pleural fluid into the peritoneal cavity or venous system [13]. Two types of pleuroperitoneal shunts have been shown to be effective. The Le Veen pleuroparitoneal shunt functions as a passive pump and Denver pleuroparitoneal shunt functions as a manual active pump [38]. By recycling nutrient-rich chyle, the bypass technique benefits the body and has been used successfully in yellow nail syndrome and post-operative chylothorax. However, these procedures are not free of complications such as surgical complications, increased risk of infection, and blockage of shunts.

One of the approaches to treating non-traumatic tumor-associated chylothorax is the irradiation of the TD [39]. In a patient with mediastinal lymphadenopathy that accompanied lymphoma, fractional irradiation of the celiac trunk and the TD with a dose of 20.4 Gy and 15 Gy, respectively, resulted in complete remission of chylothorax [40].

OUTCOMES OF CPE

Non-traumatic CPE prognoses vary depending on the etiology [7]. In benign CPE, chyle leaks are readily identified and addressed, with satisfactory results. In contrast, bilateral, malignant, and chronic chylothorax with increased nutritional loss has poor prognoses [41]. Previously, high chylothorax death rates were reported up to 50% [42]. However, aggressive treatments and healthcare facility improvements have reduced mortality rates [20]. Despite insufficient mortality statistics for non-traumatic CPE, there is optimism for improved prognosis.

CONCLUSION

CPE is characterized by an abnormal chylous fluid accumulation in the intrapleural cavity, with or without trauma to the TD. Chylothorax diagnosis requires fluid biochemical analysis. High TGs, chylomicrons, and/or cholesterol levels approve the diagnosis. Once confirmed, chylous leakage site identification and its underlying are crucial for guiding management. However, no agreed harmony exists on the appropriate CPE treatment approach. A multidisciplinary team approach is highly advisable. However, future randomized control trials are necessary to determine the most proper management strategy.

AUTHORS' CONTRIBUTIONS

All authors contributed to the completion of this work. The final manuscript was read and approved by all authors.

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