Pleural Fluid Characteristics of Chylothorax

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OBJECTIVE: **To determine the biochemical parameters of chylous pleural fluids and better inform current clinical practice in the diagnosis of chylothorax.**

PATIENTS AND METHODS: **We retrospectively reviewed 74 patients with chylothorax (defined by the presence of chylomicrons) who underwent evaluation during a 10-year period from January 1, 1997, through December 31, 2006. The biochemical parameters and appearance of the fluid assessed during diagnostic evaluation were analyzed.**

RESULTS: **The study consisted of 37 men (50%) and 37 women (50%), with a median age of 61.5 years (range, 20-93 years). Chylothorax was caused by surgical procedures in 51%. The chylous pleural fluid appeared milky in only 44%. Pleural effusion was exudative in 64 patients (86%) and transudative in 10 patients (14%). However, pleural fluid protein and lactate dehydrogenase levels varied widely. Transudative chylothorax was present in all 4 patients with cirrhosis but was also seen with other causes. The mean ± SD triglyceride level was 728±797 mg/dL, and the mean ± SD cholesterol value was 66±30 mg/dL. The pleural fluid triglyceride value was less than 110 mg/dL in 10 patients (14%) with chylothorax, 2 of whom had a triglyceride value lower than 50 mg/dL.**

CONCLUSION: **Chylothoraces may present with variable pleural fluid appearance and biochemical characteristics. Nonmilky appearance is common. Chylous effusions can be transudative, most commonly in patients with cirrhosis. Traditional triglyceride cutoff values used in excluding the presence of chylothorax may miss the diagnosis in fasting patients, particularly in the postoperative state.**

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IQR = interquartile range; LDH = lactate dehydrogenase

Chylous pleural effusions are defined by the presence of chyle in the pleural space and usually result from disruption or obstruction of the thoracic duct. These effusions were originally described in 1633 by Bartolet, and the diagnosis was initially based on the milky appearance of the fluid until the recognition that in some instances, such as in malnutrition, this characteristic appearance may be absent.[1,2] Likewise, the presence of fat globules was found to be an inconsistent feature of these effusions. The presence of chylomicrons in the fluid as demonstrated by lipoprotein electrophoresis is generally considered the criterion standard in the diagnosis of chylothorax.[2,3]

In clinical practice, the diagnosis of chylothorax is pursued when the appearance of the fluid is "milky" or when thoracic duct injury is suspected to be the cause of a pleural effusion. Although lipoprotein electrophoresis can be performed on the fluid specimen, a simpler assay of quantifying triglyceride levels is widely used to document the presence of a chylous pleural effusion. In a study performed nearly 30 years ago by Staats et al,[2] all pleural effusions with a triglyceride level greater than 110 mg/dL (to convert to mmol/L, multiply by 0.0113) proved to be chylous. Conversely, a triglyceride level less than 50 mg/dL for a pleural effusion virtually excluded the diagnosis of chylothorax. These criteria continue to be used today in the diagnosis of chylothorax.

Identifying chylothorax is crucial because it provides insight into the mechanism of pleural fluid accumulation and narrows the differential diagnosis, often dictating a change in the diagnostic approach and management.[4-7] Chylous pleural effusions are typically described as exudative lymphocytic pleural effusions with a milky appearance. However, biochemical parameters of chylous pleural effusions have been inadequately analyzed. In this retrospective study, we sought to clarify these basic aspects of chylous pleural effusions to better inform current clinical practice in the diagnosis of chylothorax.

PATIENTS AND METHODS

We conducted a computer-assisted search of the electronic medical records at Mayo Clinic's site in Rochester, MN, and identified 103 consecutive adults (≥18 years) with chylothorax diagnosed during the 10-year period from January 1, 1997, through December 31, 2006. We included only patients with chylomicrons present in the pleural fluid as demonstrated by lipoprotein analysis. Of these patients, 74 (72%) had biochemical data available for the purpose of classifying the pleural fluid as transudative or exudative. This latter cohort formed the study group.

PLEURAL FLUID DATA

Pleural effusions were classified as exudative if 1 of the following conditions was met: (1) pleural fluid protein level greater than 2.9 g/dL (to convert to g/L, multiply by

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10), (2) pleural fluid lactate dehydrogenase (LDH) level more than two-thirds of the upper limit of the normal serum value, or (3) pleural fluid cholesterol level greater than 45 mg/dL (to convert to mmol/L, multiply by 0.0259).[8] Pleural effusions were classified as transudative if none of these conditions were met or if the following 2 conditions were met: (1) pleural fluid LDH level two-thirds or less of the upper limit of the normal serum value (222 U/L; to convert to μkat/L, multiply by 0.0167) and (2) pleural fluid cholesterol level of 45 mg/dL or less.[8] The criteria described by Heffner et al[8] were chosen because they do not require simultaneous serum values, which were not consistently available in the medical records of our study participants.

Clinical Data

Medical records were examined in detail to gather clinical data, laboratory results, and radiologic data. The cause of chylothorax was assigned to each case by consensus of 2 of the authors (F.M., J.H.R.) after all available medical records were reviewed for each case. Symptom duration was defined as the period from the patient's first recollection until diagnostic evaluation at Mayo Clinic's site in Rochester, MN. All laboratory testing was performed at Mayo Clinic laboratories in Rochester, MN.

Statistical Analyses

Data are presented as mean ± SD and select percentiles for continuous variables and percentages for categorical variables. The demographic and clinical data among patients were compared using the Fisher exact test and Wilcoxon rank sum test. $P<.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Features

The 37 men (50%) and 37 women (50%) had a median age of 61.5 years (range, 20-93 years). Pleural effusion was unilateral in 58 patients (78%). Of these 58 patients, the effusion involved the right hemithorax in 39 (67%) and the left hemithorax in 19 (33%). Pleural effusion was bilateral in the remaining 16 patients (22%).

Surgical procedures were the cause of chylothorax in 38 patients (51%). These procedures included thoracotomy with lung resection and mediastinal lymphadenectomy (16 patients), lung resection without mediastinal lymphadenectomy (5 patients), posterior mediastinal tumor resection (2 patients), and extrapleural pneumonectomy with pericardiectomy (1 patient). Other surgical procedures were Ivor-Lewis esophagogastrectomy with thoracic lymphadenectomy (5 patients), pericardiectomy (2 patients), left subclavian artery stenosis repair (1 patient), abdominal aortic aneurysm repair (1 patient), heart transplant (1 patient), coronary artery bypass grafting (1 patient), median sternotomy for thymic tumor (1 patient), aorta to superior mesenteric artery bypass (1 patient), and thoracolumbar vertebral fusion (1 patient).

Nonsurgical causes of chylothorax were noted in 29 patients (39%) and included lymphoproliferative disorders (9 patients), thoracic duct thrombosis (4 patients; 2 whose conditions were attributable to complications of central venous catheterization, 1 whose condition was attributable to thoracic outlet syndrome, and 1 with an unknown cause), solid tumors (4 patients), cirrhosis of liver (4 patients), radiation injury (3 patients), lymphatic disorders (3 patients), lymphangioleiomyomatosis (1 patient), and amyloidosis (1 patient). The cause of chylothorax could not be identified in the remaining 7 patients (9%).

Pleural Fluid Characteristics

Gross appearance of the pleural fluid was documented in the medical records for 61 patients and was described as milky (27 patients [44%]), serous (16 patients [26%]), serosanguinous (16 patients [26%]), or bloody (2 patients [3%]). No obvious pattern of association was found between the gross appearance of the pleural fluid and the cause, except for bloody pleural effusions, which both occurred in postsurgical patients.

On the basis of biochemical criteria, 64 patients (86%) had exudative effusions, and 10 (14%) had transudative effusions. Of 10 transudative pleural effusions, 9 met all 3 criteria (low protein, LDH, and cholesterol values); 1 was classified on the basis of low LDH and cholesterol levels (pleural fluid protein level was not available). The broad distribution of total protein and LDH values is shown in Figure 1 and Figure 2, respectively. The causes of the 10 transudative pleural effusions were as follows: liver cirrhosis (4 patients), surgical procedures (2 patients), lymphoproliferative disorder (1 patient), pancreatic cancer (1 patient), radiation injury (1 patient), and idiopathic (1 patient). The mean ± SD triglyceride value for transudative chylothoraces was 192.4±105.5 mg/dL, with a median of 195 mg/dL (interquartile range [IQR], 135-238.5 mg/dL). Most postsurgical chylothoraces were exudative (36 [95%] of 38 patients). The mean ± SD triglyceride value for exudative chylothoraces was 855.3±816.3 mg/dL, with a median of 601.5 mg/dL (IQR, 210.5-1050.0 mg/dL).

Overall, the mean ± SD triglyceride level was 728±797 mg/dL (median, 483.5 mg/dL; IQR, 200-936 mg/dL), and the mean cholesterol value was 66±30 mg/dL (median, 60 mg/dL; IQR, 49.5-85.5 mg/dL). Ten pleural effusions (14%) had a triglyceride level lower than 110 mg/dL, with 2 of these being less than 50 mg/dL (Figure 3). The causes of chylothoraces with a triglyceride level less than 50 mg/dL

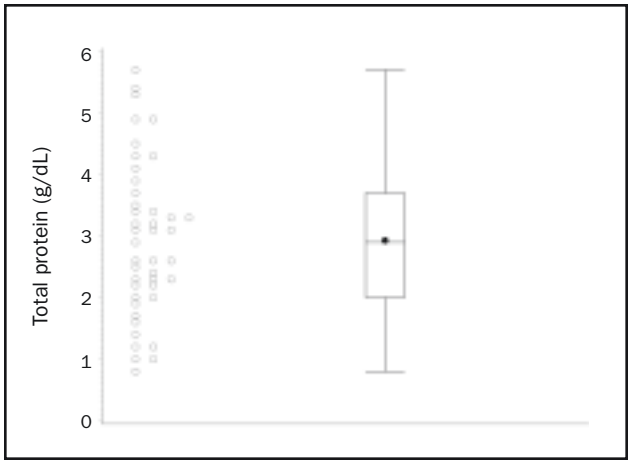

FIGURE 1. Pleural fluid total protein values in 43 patients with chylothorax. Boxes show interquartile ranges, and error bars represent highest and lowest values. The mean ± SD total protein level was 2.49±1.26 g/dL (median, 2.90 g/dL; interquartile range, 2.0-3.7 g/dL).
SI conversion factor: To convert to g/L, multiply by 10.

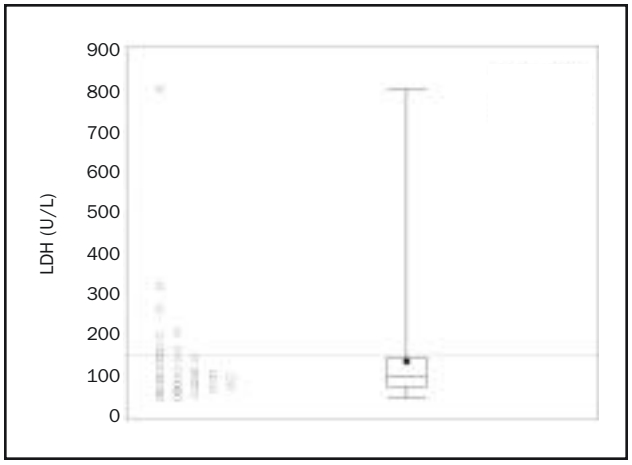

FIGURE 2. Pleural fluid total lactate dehydrogenase (LDH) values in 74 patients with chylothorax. Horizontal hashed line denotes two-thirds of the upper normal limit for serum LDH value (ie, threshold between exudate and transudate by LDH criterion). Boxes show interquartile ranges, and error bars represent highest and lowest values. The mean ± SD total LDH level was 133.6±133.3 U/L (median, 96.5 U/L; interquartile range, 71-144 U/L).
SI conversion factor: To convert LDH values to μkat/L, multiply by 0.0167.

were surgery (Ivor-Lewis procedure, transudate) and thoracic duct tear from central venous catheterization (exudate).

Data on the cellular constituents of the pleural fluid analysis were available in 30 patients (41%). The total and differential cell counts were available for 6 transudative effusions. The mean ± SD number of nucleated cells was 208±201 cells/mL. One transudative pleural effusion had a lymphocyte percentage greater than 50% (ie, lymphocytic pleural effusion [chylothorax was secondary to cirrhosis]). Neutrophilia (57%) was noted in 1 transudative effusion (chylothorax secondary to Ivor-Lewis esophagogastrectomy).

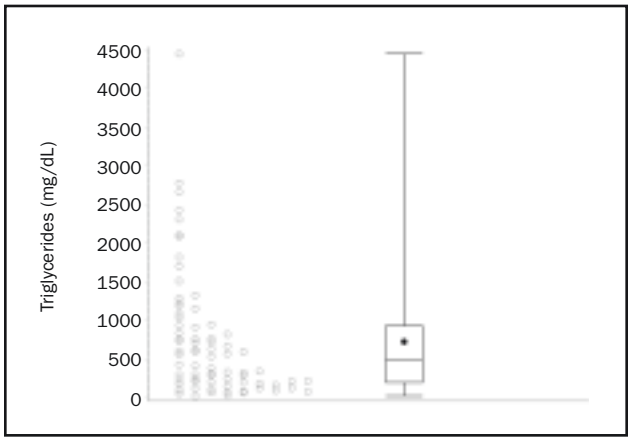

FIGURE 3. Pleural fluid total triglyceride values in 74 patients with chylothorax. Boxes show interquartile ranges, and error bars represent highest and lowest values. The mean ± SD total triglyceride level was 728±797 mg/dL (median, 483.5 mg/dL; interquartile range, 200-936 mg/dL).
SI conversion factor: To convert total triglyceride values to mmol/L, multiply by 0.0113.

Cell counts were available for 24 exudative pleural effusions. The mean ± SD number of nucleated cells was 1775±2369 cells/mL. The differential cell count was available for 23 patients. Most postsurgical chylothoraces (5/7 patients) contained a predominance of neutrophils. Thirteen exudative chylothoraces were lymphocytic (>50% lymphocytes) and were found in patients with non-Hodgkin lymphoma (3 patients), lymphatic dysplasia (2 patients), thrombosis of the subclavian vein (2 patients), and surgery (2 patients). The chylothorax was idiopathic in the remaining 4 patients with lymphocytic effusions.

Biochemical parameters of milky (n=27) and nonmilky (n=34) chylous pleural effusions were compared. Three milky effusions (11%) were transudative compared with 7 nonmilky effusions (21%), a difference that was not statistically significant (P=.49). Similarly, no statistically significant difference was noted in LDH (P=.80), protein (P=.26), or cholesterol levels (P=.33). However, the median triglyceride level was significantly higher in milky effusions (822 mg/dL) compared with nonmilky effusions (241 mg/dL) (P<.001).

DISCUSSION

In the current study, gross appearance of the fluid was not a sensitive diagnostic criterion in identifying chylothorax. Less than half of chylous pleural effusions (44%) had the

classic milky appearance attributed to chylothorax. This finding likely relates to the variable lipid content of the effusion, a direct consequence of the nutritional status of the patient. In some cases, another factor may have contributed to the formation of pleural effusion (eg, surgical trauma). Gross appearance of the pleural fluid did not correlate with any particular cause except for bloody pleural effusions that were found after surgery. Variable gross appearance of chylous pleural fluid was noted previously by Staats et al[2]; however, serous or serosanguinous appearance was more common in the current study, being observed in half the patients. Milky effusions had significantly higher levels of triglycerides compared with nonmilky effusions, although other fluid characteristics (protein, LDH, and cholesterol levels) were similar. Some cases of chylothorax are likely undiagnosed in clinical practice because of their nonmilky appearance.

Most chylous pleural effusions in our study were classified as exudative (64/74 pleural effusions) by currently used biochemical criteria.[9,10] This is an interesting finding because protein concentrations in chyle have been reported to be 2 to 3 g/dL, and chylous pleural effusions are expected to be transudative.[11] A recent report[11] suggested that chylous pleural effusions may become exudative as the protein level increases due to fluid reabsorption from the pleural to the intravascular space. The LDH level in chyle is relatively low, and the LDH level in the chylous pleural fluid generally remains in the transudative range. An elevated LDH level should suggest an additional mechanism for the pleural effusion other than a mere chyle leak.[11] In our study, only 8 exudative pleural effusions exhibited an LDH level in the exudative range, and although limited by its retrospective nature, careful review of the medical records showed no additional diagnoses in these patients.

Transudative chylous pleural effusions are uncommon. A review published in 2005 identified only 13 cases of transudative chylous pleural effusions reported in the literature.[9] Typical causes of such effusions included hepatic cirrhosis, nephrotic syndrome, amyloidosis, and obstruction of the superior vena cava. In the current series, 10 transudative chylous effusions were found, with the most common cause being hepatic cirrhosis.[10] Chylothorax that occurs with cirrhosis may result from functional obstruction of the thoracic duct secondary to increased intra-abdominal pressure due to accumulation of ascites, a consequence of extremely elevated portal pressures. The combination of transudative ascites from portal hypertension and chylous ascites may eventually result in lower levels of protein, LDH, and cholesterol in the pleural fluid as the peritoneal fluid translocates from the abdominal to the thoracic cavity. In the current study, 4 transudative effusions were secondary to cirrhosis and 1 to pancreatic cancer with evidence of portal hypertension.

The cellular profile of the chylous effusions was available in less than half of the patients, and the limited data make it difficult to draw any conclusions. However, lymphocytic predominance was not a universal finding, particularly in transudative pleural effusions.

The currently used biochemical criterion for chylothorax was introduced nearly 30 years ago by Staats et al,[2] who found a pleural fluid triglyceride level greater than 110 mg/dL to be a relatively accurate marker for the presence of chylothorax. According to their data on 38 patients with chylothorax, a pleural fluid triglyceride level greater than 110 mg/dL was associated with a less than 1% chance of not being chylous. Conversely, a pleural fluid triglyceride level less than 50 mg/dL indicated no more than a 5% chance of being chylous. In our study, 14% of chylothoraces were associated with a total triglyceride level less than the traditional cutoff value of 110 mg/dL; 2 of these effusions had a triglyceride level lower than 50 mg/dL. Four of these effusions occurred after surgery; one could hypothesize that perioperative fasting may have accounted for the low triglyceride levels. In addition, 1 patient with pancreatic cancer was malnourished. Three other chylous pleural effusions with low triglyceride levels were complications related to central venous line placement in patients with critical illnesses and malnourished states. Thus, in fasting and malnourished patients, reliance on the triglyceride criteria may result in the diagnosis of chylothorax being missed.[2,3,5]

The main limitation of the current study is its retrospective design. Not all pleural fluid parameters were available in every patient with chylothorax. Thus, we included only those patients in whom pleural fluid data were adequate to enable classification of the pleural effusion as exudate or transudate. For example, 25 of 29 individuals excluded from the current study because of lack of pleural fluid biochemical data had undergone surgery (mostly the Ivor-Lewis procedure) with obvious chyle leak for which they were promptly taken back to the operating room for repair. The exclusion of such cases may have increased the frequency of atypical characteristics. In addition, the overall number of patients in the study was modest because chylothorax is an uncommon form of pleural effusion. As previously observed,[12] the high number of postsurgical chylothorax cases may directly reflect the larger number of cardiothoracic surgical procedures performed at our institution, which may limit the generalizability of our results.

CONCLUSION

Chylothoraces may present with variable pleural fluid appearance and biochemical characteristics. Nonmilky ap-

pearance is a common presentation and may cause the diagnosis of chylothorax to be overlooked. Chylous effusions may be associated with a wide range of total protein and LDH values, sometimes resulting in a transudative character by currently used criteria. Because triglyceride levels also vary in patients with chylothorax, traditional triglyceride cutoff values used in excluding the presence of chylothorax may miss the diagnosis in fasting patients, particularly in the postoperative state.

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