

Chylothorax in Patients With Chronic Lymphocytic Leukemia: A Case Series

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Abstract

Chylothorax, which is defined as the presence of chyle in the pleural space, is often caused by malignancy. However, chylothorax as a result of underlying chronic lymphocytic leukemia (CLL) is exceedingly rare in the literature. Chyle contains fat soluble vitamins and lymphocytes, meaning that its collection into the pleural space may further exacerbate the immunosuppressed state of an individual with CLL. Here, we report three cases of patients with CLL who developed chylothorax, and their management. Chylothorax, although rare with CLL, should be considered in the differential diagnosis when patients with CLL present with pleural effusions, especially if recurrent. Discovery of a chylothorax may indicate the need for further treatment of CLL.

Keywords: Chylothorax; Chronic lymphocytic leukemia

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western Hemisphere. During the course of the disease, CLL patients may develop thoracic complications including pleural effusions. However, most of the reported literature describes pulmonary complications related to pneumonia [1]. There is scant literature describing pleural effusions related to CLL. Here, we report the outcomes of three cases in which patients with CLL were found to have chylous effusions at varying stages of disease.

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Chylous pleural effusions are defined by the presence of chyle (a lymphocyte rich fluid) accumulating in the pleural space, often secondary to disruption or obstruction of the thoracic duct [2, 3]. Chyle will accumulate in the right pleural space if the disruption occurs below the fifth thoracic vertebra, however if the thoracic duct is disrupted above the fifth thoracic vertebra, the chylothorax will typically occur in the left pleural space [4, 5]. The majority of chylous effusions are unilateral and on the right side.

Chylothorax is caused either by malignancy, which represents about half of all cases, trauma, which accounts for about a third of cases, or other miscellaneous conditions including sarcoid, tuberculosis, lupus, lymphangiomyomatosis and cirrhosis, which collectively make up about 14% of cases [6]. While malignancy accounts for about half of all chylothoraces, there have only been 12 reports of chylothorax related to CLL [6].

Case Reports

Case 1

A 78-year-old male with a remote history of hairy cell leukemia treated with interferon and cladribine, prostate cancer (Gleason 4+5, treated with prostatectomy and hormonal manipulation and then abiraterone upon progression), diastolic congestive heart failure (CHF) and CLL with 13q deletion (see Table 1 for detailed prognostic markers) and associated hypogammaglobulinemia, presented with recurrent shortness of breath. Prior to developing shortness of breath, his CLL had been observed clinically for 5 years before his white blood cell count (WBC) rose to $220 \times 10^9/L$ and he developed dyspnea on exertion. At the time, as none of the novel targeted agents were commercially available, he was started on pentostatin, cyclophosphamide and rituximab (PCR) for two cycles. Additionally he was given furosemide for dyspnea and bilateral pleural effusions presumed secondary to CHF. Following completion of his second cycle of PCR, his shortness of breath worsened and a computed tomography (CT) scan showed increased bilateral pleural effusions, which persisted despite treatment with diuretics. Therapeutic thoracentesis yielded a turbid, yellow exudative effusion with an elevated triglyceride count of 347 mg/dL consistent with a chylothorax. Pleural fluid flow cytometry yielded fluid with a mono-

Table 1. Patient Characteristics

Patient	Age at presentation of chylothorax/sex	Cytogenetics	IGHV status	Other prognostic markers	Treatments	Symptoms	Outcome
Patient 1	78/M	13q deletion	Unmutated	CD38 (-); Zap70 (-)	Interferon; cladribine; pentostatin, cyclophosphamide and rituximab; bendamustine and rituximab	Shortness of breath	Bendamustine and Rituxan × two cycles: developed recurrent effusions 2 years post therapy; ibrutinib: tolerated for 5 months with good response before developing atrial fibrillation; PleurX catheterization; obinutuzumab with ibrutinib: approximately 5 months with therapy complicated by atrial fibrillation and bloody pleural effusions; idelalisib: tolerated for 3 weeks and discontinued due to grade III psoriatic type rash; ibrutinib was re-challenged but due to recurrent infection and effusions, he elected for home hospice.
Patient 2	81/F	11q deletion	Unknown	CD38 (+)	Bendamustine and Rituxan	Shortness of breath	Marginal improvement after bendamustine and Rituxan (three cycles) developed worsening chylous effusions and deferred further therapy and expired due to pulmonary complications
Patient 3	77/F	13q deletion	Mutated	CD38 (-)	Obinutuzumab × 1 cycle; 2,400 cGy RT	Shortness of breath	Improved after 2,400 cGy to thoracic duct and mediastinum

IGHV: immunoglobulin heavy chain variable region genes; RT: radiation therapy.

clonal B cell population expressing cluster of differentiation (CD)19, dim CD20, CD5, and CD23 markers, consistent with CLL (Table 2).

Initially the patient was recommended to undergo placement of a long term indwelling catheter [7] or video-assisted thorascopic surgery with pleurodesis for management of his effusions. However, once the diagnosis of chylothorax was made in the setting of CLL the decision was to change CLL-directed treatment to bendamustine and Rituxan for two cycles with improvement in the quantity of the effusions. He did not

require treatment again for over 2 years upon development of worsening adenopathy. At recurrence, recently approved ibrutinib was started. Single agent therapy was tolerated for 5 months until he developed new onset atrial fibrillation. In light of worsening effusions off of therapy, the patient had a PleurX catheter placed followed by the initiation of obinutuzumab combined with ibrutinib. Combination therapy was complicated by recurrent atrial fibrillation and eventual development of recurrent serosanguineous pleural effusions requiring therapy discontinuation. Approximately 1 month after discontinuation,

Table 2. Fluid Characteristics

Patient	Color	Pleural fluid nucleated cell count (cell/ μ L)	Pleural fluid RBC count (cell/ μ L)	Pleural fluid glucose	Fluid/serum protein	Fluid/serum albumin	Fluid/serum LDH	Pleural fluid triglycerides
Patient 1	Yellow, cloudy	120	8,875	112	3.3/5.8	2.8/4.2	122/194	347
Patient 2	Cream colored, turbid	210	860	236	5.1/6.5	2.9/3.2	147/275	n/a
Patient 3	Cream colored	n/a	n/a	113	2.2/4.5	1.6/3.1	319/415	311

RBC: red blood cell; LDH: lactate dehydrogenase.

his pleural effusions recurred causing recurrent symptoms. At this time, given recurrent atrial fibrillation, he was treated with idelalisib. The patient developed a significant grade III psoriatic type rash requiring discontinuation of the drug only 3 weeks after its initiation. Six weeks later he again developed worsening effusions causing dyspnea and he was rechallenged with ibrutinib. While on ibrutinib therapy he developed recurrent staphylococcal empyemas coupled with worsening pleural effusions. In light of significant debilitation and infectious complications he was referred to home hospice where he later expired.

Case 2

An 81-year-old female with no previous diagnosis of malignancy initially presented with cough, dyspnea on exertion and a 40 pounds weight loss over several months. Physical exam revealed bilateral cervical and axillary adenopathy as well as decreased breath sounds and dullness to percussion over the bilateral lower lung fields. A complete blood count was normal without any cytopenias and a normal lymphocyte count. A CT scan of her chest revealed a large right and moderate left pleural effusion as well as extensive axillary, mediastinal, hilar adenopathy. Thoracentesis yielded 2 L of a classic milky appearing exudative effusion, however a triglyceride level was not sent on this specimen. Cytology and flow cytometry showed a small population of monoclonal B cells in a background of polymorphous lymphocytes with a few atypical lymphocytes (Table 2). This led to an axillary lymph node biopsy consistent with CLL.

Chemotherapy was recommended and the patient completed three cycles of the bendamustine and rituximab. Post-chemotherapy CT scans showed a partial response with decrease in adenopathy; however, moderate pleural effusions remained. Due to persistent symptoms of dyspnea on exertion, another thoracentesis was performed which was again chylous in appearance. Despite the improvement in adenopathy the continued chylous effusion suggested persistent disease and further treatment was recommended. The patient deferred treatment and she presented to the emergency room with hyponatremia and large bilateral pleural effusions causing respiratory failure. Despite aggressive measures and repeat large volume thoracentesis confirming chylothorax, the patient passed away of pulmonary complications.

Case 3

A 77-year-old female, originally diagnosed with CLL in 2009, was being followed clinically until she developed worsening anemia and thrombocytopenia in 2015. At that time, she also complained of shortness of breath and began treatment with obinutuzumab monotherapy. After one cycle of treatment, she was admitted to the hospital for worsening shortness of breath. She was noted to have bilateral pleural effusions. The effusions were drained and were consistent with a chylous effusion with a triglyceride level of 311 mg/dL (Table

2). Her effusions recurred and an indwelling pleural catheter was placed on the right side, which drained 700 mL to 1 L of fluid daily. She was started on idelalisib to better control her disease but she continued to have significant pleural fluid drainage. After 2 months of treatment with idelalisib, she was found to have an empyema growing *S. sanguinis* which required 6 weeks of ceftriaxone. Given ongoing serious infection, idelalisib was discontinued and radiation treatment was pursued. She received 2,400 cGy of radiation in 12 fractions to her thoracic duct and mediastinum. After radiation, her effusions improved and the patient has remained off systemic treatment for the past 17 months.

Discussion

CLL can present with diffuse lymphadenopathy, however mediastinal lymphadenopathy severe enough to obstruct the thoracic duct is rare [8-10]. CLL diagnosis is not traditionally associated with chylothorax [11], although other types of pleural effusions may occur more commonly with long standing CLL [12]. Some of the proposed mechanisms for CLL induced chylothorax include the possibility that large amounts of abnormal lymphocytes in CLL may cause sludging in the lymphatic system, resulting in a pseudo-obstruction of the thoracic duct or lymphatics draining the pleura, or that the sludging may lead to distention of the thoracic duct making it more susceptible to rupture causing chyle to leak into the pleural space [5].

Chylothorax typically presents as an exudative effusion with a milky white appearance, however this is not a reliable diagnostic marker. A recent retrospective analysis of 74 patients previously diagnosed with chylothorax found only 44% to have a milky white appearance. Lack of the classic milky white appearance may occur in some instances of malnutrition, which may occur in patients with advanced disease [13]. The characteristic feature of a chylous effusion is an elevated triglyceride level which is present whether the effusion is milky or not, and can differentiate it from other milky effusions such as a cholesterol effusion. Chylous effusions are generally exudative, however about 15% are transudative in nature [13]. A triglyceride concentration of more than 110 mg/dL, or the presence of chylomicrons in the pleural fluid has been established as the criteria to confirm the presence of a chylothorax [2, 13]. In a study performed by Staats et al, all pleural effusions reviewed with a triglyceride level greater than 110 mg/dL were found to be chylous, while a triglyceride level less than 50 mg/dL excluded the diagnosis [14]. In cases suggestive of a chylous effusion where the triglyceride level is between 50 and 110, a lipid electrophoresis to detect the presence of chylomicrons can be performed.

As with other types of pleural effusion, dyspnea and orthopnea are the most common symptoms of chylothorax. Chest pain or infection are less frequent presenting symptoms as chyle is bacteriostatic and is not irritating to the pleura. In addition to respiratory complications, chylothorax is associated with malnutrition and immunosuppression [15]. Chyle contains fat soluble vitamins and a significant amount of dietary calories from fat intake. There are also lymphocytes present in

the fluid, and as chyle leaks into the pleural space, these substances are lost, predisposing the patient to immunodeficiency and malnourishment. In a patient with CLL, who is already immunosuppressed and often hypogammaglobulinemic, this can become a significant concern and should be considered a factor when deciding therapeutic options for the management of CLL.

Therapy to decrease the complications of chylous effusions aims to treat the underlying condition. Additionally there are conservative surgical interventions, which can help improve the patient symptoms. Conservative management entails draining the effusion, either by thoracentesis or long term indwelling catheter, repleting lost nutrients along with the institution of a low fat, medium-chain triglyceride diet. This diet contains fats that are directly absorbed into the portal system, bypassing the intestinal lymph system [16]. Repeated pleural drainage can treat the symptoms related to the effusion, but continued chyle drainage effectively depletes proteins and lymphocytes, thus negatively impacting the immune system [15, 17]. The surgical options include video-assisted thorascopic procedures with pleurodesis to cause adhesion of the visceral and parietal pleura or a more invasive pleurectomy which involves complete decortications of the visceral and parietal pleura [18]. Surgical therapy is less common as medical thorascopic talc pleurodesis has been shown to have very good success rates, with minimal complications in the prevention of recurrent pleural effusions in patients with chemotherapy and/or radiation therapy refractory lymphoma [15].

Pleuroperitoneal shunt has been proposed as an alternative to more invasive surgery and has been effective in resolving chylothorax in small case series. Pleuroperitoneal shunting has been used as an option for palliation of dyspnea by decreasing pleural fluid levels, while allowing the chyle to flow into the peritoneal cavity where it may be absorbed, allowing for some retention of nutritional and immunological value. Shunting also appears to cut hospital costs, decrease iatrogenic complications and decrease symptoms, without subjecting the patient to a thoracotomy [6, 15]. However, shunts are falling out of favor due to difficulties with shunt failure, often due to shunt occlusion or infection. None of the patients with CLL had this therapeutic modality due to infection risk concerns.

Ligation of the thoracic duct is another intervention that has been reported to successfully resolve a chylothorax related to CLL, although the patient outlined in the cited case report received thoracic duct ligation in combination with pleurodesis [9]. Finally, radiotherapy has also been reportedly used with successful resolution of refractory chylothorax, as described in the case above. This has also been reported in a patient with advanced follicular non-Hodgkin's lymphoma and bulky lymphadenopathy of the thoracic trunk [19]. In this case, there was improvement of chylothorax after 7.5 Gy of radiotherapy, and complete resolution after 20.4 Gy of radiotherapy, with no recurrence at 17 months of follow-up.

However, in patients with CLL who are found to have chylous effusion the answer may be to treat the underlying CLL, although the optimal CLL directed management is unclear. Chylous effusions appear to be an indicator of progressive or worsening CLL and treatment of the underlying source, the

CLL, is what will be of most benefit to the patient. The role of recently approved targeted agents such as ibrutinib and idelalisib is yet unclear as these patients were excluded from participation in clinical trials on the basis of their effusions. In the only patient that received commercially available targeted agents, he had symptomatic relief however therapy had to be discontinued due to treatment-emergent toxicities.

Conclusions

In this case series, we present three patients with CLL who presented with pleural effusions which were noted to be chylous in etiology. Chylous effusions may be caused by malignancy, however they are rarely found in patients with a CLL diagnosis. Common therapies to ease symptoms include thoracentesis, diet modification, talc pleurodesis, and indwelling pleural catheters. Pleuroperitoneal shunting, thoracic duct ligation and radiotherapy are less common interventions. Given that chyle contains significant quantities of lymphocytes as well as fat soluble vitamins, it is important to entertain the possibility of a chylothorax in the workup of a pleural effusion in patients with CLL, as this diagnosis should factor into the clinicians overall treatment decision making process and initiation of treatment for CLL.

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