

## CHYLOTHORAX AS RARE MANIFESTATION OF PLEURAL INVOLVEMENT IN WALDENSTRÖM MACROGLOBULINEMIA: MECHANISMS AND MANAGEMENT

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### ABSTRACT

*Here we report the clinical, pathological, and immunological features of a rare case of Waldenström macroglobulinemia (WM) with pleural infiltrations. An atypical chylothorax, successfully treated by videothoracoscopy, represented the main clinical feature of this case of low-grade lymphoplasmacytic lymphoma. Pleuropulmonary manifestations are rare (from 0 to 5% of cases) in WM, with chylothorax observed in just seven patients worldwide. In addition to describing this uncommon clinical presentation, we investigate hypothetical pathogenetic mechanisms causing chylothorax and through an up-to-date review of available literature furnish helpful suggestions for diagnosis and management of chylothorax in WM patients.*

**Keywords:** Waldenström macroglobulinemia, chylothorax, thoracic duct, pleural effusion, talc pleurodesis, videothoracoscopy

Waldenström macroglobulinemia (WM) is a rare B-cell malignancy representing about 2% of hematologic malignancies (1,2). It is characterized by proliferation of a cell population consisting of lymphoplasmacytoid cells and associated with a monoclonal

increase of IgM level. Pleuropulmonary involvement is reported to be rare (from 0 to 5% of cases), and it usually occurs during the late phase of the disease (3,4). In such a scenario, chylothorax is rarely observed in WM patients; indeed only seven cases have been reported in the literature (5-11). We report the case of a 66-year old man with the main clinical presentation of pleural infiltrations with right chylothorax following immunochemotherapy. An extra-bone marrow involvement was suggested by both pleural fluid examination and multiple pleural biopsies in parallel with a marked decrease of bone marrow (BM) participation (tumor cells in BM from 70% to 8%). The resulting chylothorax was resistant to medical therapies, but it was successfully treated by videothoracoscopy.

### CASE HISTORY

A 66-year old man with a history of hypertension and colon cancer (treated with sigmoid resection plus chemotherapy) presented with an immunoglobulin M (IgM)  $\lambda$  (lambda) M-spike on serum protein electrophoresis and a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) made in 2008. In 2010, during



*Fig. 1. CT scan shows the right pleural effusion which is still large despite numerous thoracenteses. Pleural thickening is evident posteriorly along the costovertebral space (asterisk) and in the prevertebral plane with contralateral extension (arrowhead).*

follow-up examination, marrow biopsy revealed a small lymphocytic infiltrate in approximately 20-30% of the total population. Renal function and calcium level were normal apart from mild proteinuria attributed to the long-lasting hypertension history. Lytic lesions or hepatosplenomegaly were absent. The patient denied any symptoms, his appetite was good, and no weight loss was documented during last months. Based on these findings, a diagnosis of low-grade B lymphoma with an IgM monoclonal component was made.

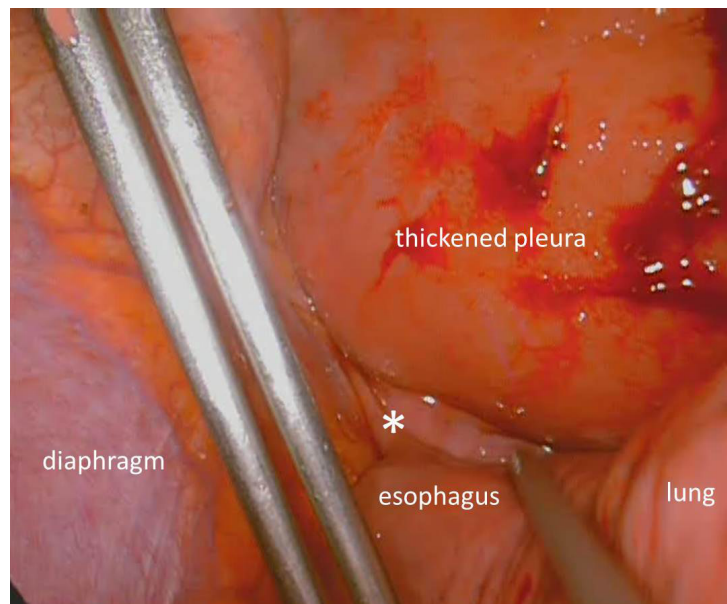
During the following months, a progressive IgM serum level and free light chains increase were observed in parallel with progressive impairment of renal function. A bone marrow biopsy repeated in 2013 showed a replacement of the normal cellular population by 60%-70% of the lymphoplasmacytic infiltrate. Likewise, a renal biopsy showed a lymphoid infiltrate indicating kidney involvement by lymphoplasmacytic lymphoma. An allele-specific

polymerase chain reaction for MYD88L265P confirmed the diagnosis of WM. Otherwise, abdominal ultrasound showed neither hepatosplenomegaly nor lymphadenopathy, and CT total body and PET/CT scans were not performed. Collectively these data supported the diagnosis of WM with renal involvement. Accordingly, from April to July 2013 the patient was treated with 6 doses of rituximab plus cyclophosphamide and prednisone. The therapy was well tolerated although fatigue and dyspnea occurred at the end of the first cycle and persisted during the entire course of treatment. Due to dyspnea worsening, a chest x-ray was carried out at the end of therapy displaying pleural effusion on the right side. As a result, two serial thoracenteses were performed and approximately 1900 mL of opaque milky fluid was obtained. Based on triglycerides and cholesterol concentration (1197 mg/dl and 119 mg/dl, respectively), the diagnosis of chylothorax was made. In parallel, chest and abdomen CT scan showed persistence of pleural effusion on the right side together with parietal pleura thickening (*Fig. 1*). No hepatosplenomegaly, or enlarged mediastinal or abdominal lymphadenopathy were evident. During the subsequent two months, further thoracenteses were performed.

In 2014, a remission of WM was observed. Indeed, blood tests were normal although a slight IgM level increase was observed in serum proteins, and bone marrow biopsy showed a lymphocytic infiltrate accounting for about 8% of the cellular population. A pleural drainage was also performed obtaining about 2000 mL of chyle. A subsequent lymphangiogram showed normal abdominal lymphatic pattern, with cisterna chyli and thoracic duct normal during their entire course till termination at the left supraclavicular space (*Fig. 2*). However, a slight contrast leakage appeared to be present cephalad to the cisterna chyli at the emergence of the thoracic duct into the chest. This finding was confirmed by CT scan (*Fig. 2*). PET/CT scan further corroborated presence



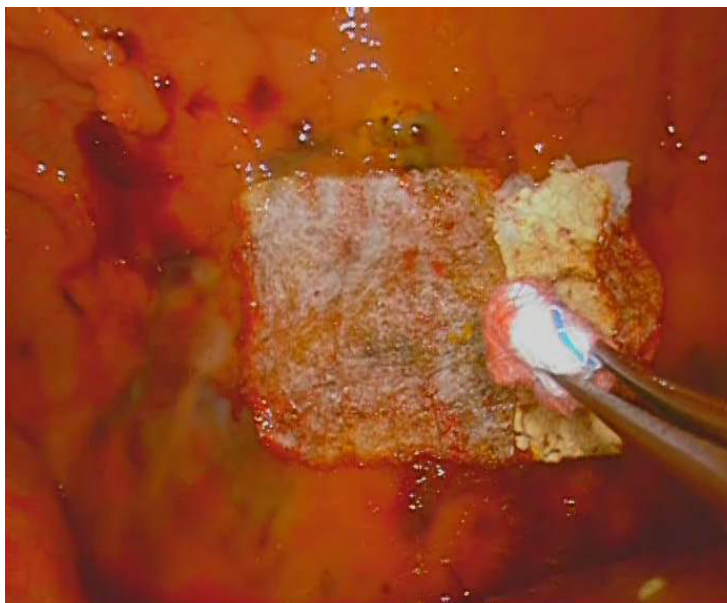
*Fig. 2. CT scan performed after lymphangiography. The thoracic duct arises in the mediastinum with typical caliber and course. The cisterna chyli and thoracic duct origin are highlighted by circles and an arrow indicates the location of potential minimum leakage (\* identifies chest tube).*



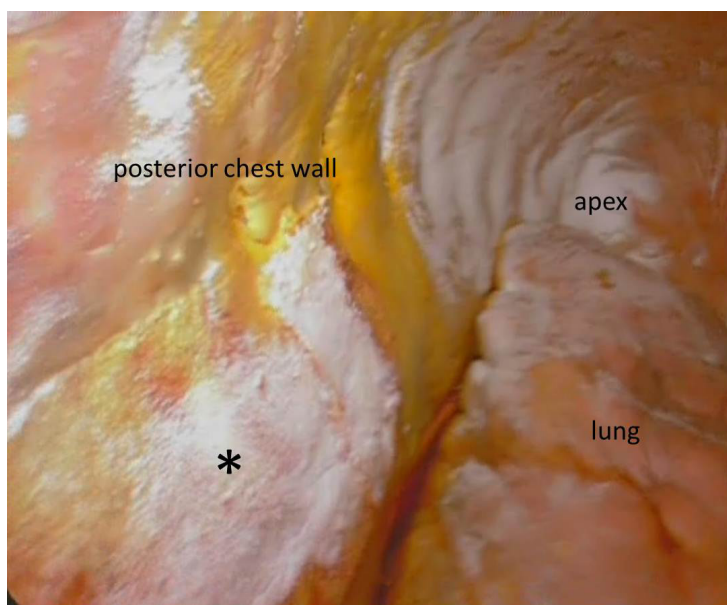
*Fig. 3. Videothoroscopic view of right costovertebral angle and diaphragmatic sinus (asterisk) (frontal view).*

of thickened pleura at the right paravertebral space from D4 to D12 associated with its enhanced metabolic activity (SUV max of 3,8). Finally, flow cytometry analysis on pleural fluid revealed pleural localization of B-lymphoplasmocytic non-Hodgkin lymphoma with an IgM $\lambda$  component. Based on these findings, conservative treatment of the chylothorax, with fasting, total parenteral nutrition, and subcutaneous octreotide

was started. Although fluid became clearer, persistence of 400-500 mL daily leak was continually observed even after seven days. Therefore, a videothoracoscopy was undertaken. A fatty meal was administered three hours prior to surgery. The pleura was diffusely hyperemic, and a small amount of opalescent fluid was aspirated. A wide area of opalescent and thickened pleura was evident posteriorly down to the diaphragm-



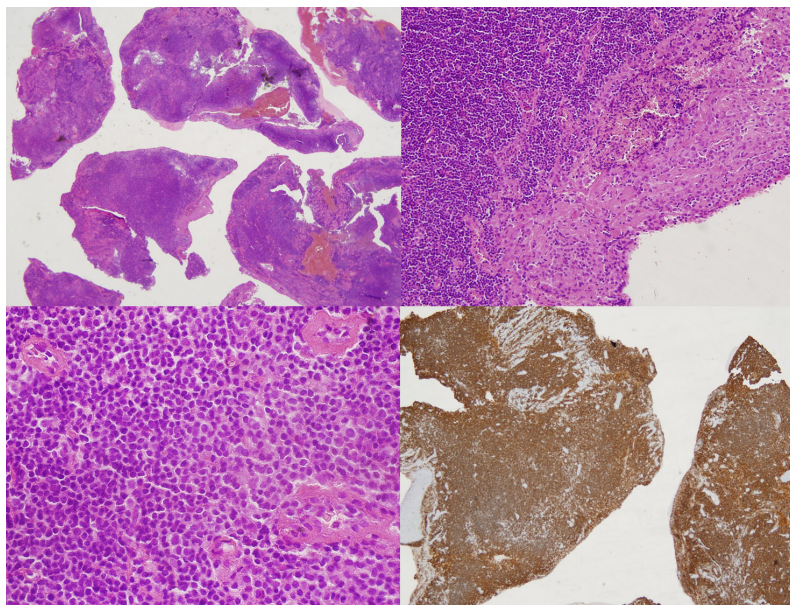
*Fig. 4. TachoSil® (Takeda UK Ltd) was used as a lymphostatic patch.*



*Fig. 5. Once insufflated using thoracoscopy, talc distributes uniformly on pleural surface allowing optimal pleurodesis and inhibiting further pleural collections. The asterisk indicates the patch of TachoSil® (Takeda UK Ltd).*

matic sinus (Fig. 3). The diaphragm was retracted and the pulmonary ligament was exposed. No macroscopic chylous leak was evident. Multiple biopsies were made. To

prevent possible major lymphatic leakage from biopsy sites, a patch of TachoSil® (Takeda UK Ltd) was used (Fig. 4). Next, pleurodesis was performed by using 6 grams



*Fig. 6. Histology revealed diffuse pleural involvement with neoplastic infiltrate composed predominantly of small lymphocytes (CD20<sup>+</sup>) mixed with variable numbers of plasmacytoid lymphocytes and plasma-cells. Often, mainly in extranodal sites, small-B cell lymphomas and plasmacytic neoplasms are difficult to identify. In our case, clinical and laboratory findings supported the diagnosis of lymphoplasmacytic lymphoma.*

of talc, insufflated and uniformly distributed on the pleural surface through a gas-propelled disposable atomizer (Steritalc®; Novatech, La Ciotat, France) (Fig. 5). Finally, a 28-French chest tube was imbedded and connected to 20 cm H<sub>2</sub>O pressure for 72 hours. At the end of this period, a low-fat diet was started. In the following 72 hours, less than 100 mL of clear fluid was drained daily and the chest tube was removed. Histology was consistent with pleural localization of lymphoplasmacytic lymphoma (Fig. 6). After 1 month, a CT scan of chest and abdomen was performed, showing persistence of thickening in the right parietal pleura and absence of pleural effusion. Follow up visits were done at three, six, and 12 months and the patient continues to be asymptomatic and chest x-ray confirms that the pleural cavity completely free of effusion. Based on WM diagnosis, a “watch and wait” policy was chosen for the management of this patient.

#### DISCUSSION

Waldenström macroglobulinemia is a rare disease. An annual age-adjusted incidence of 0.38 per 100,000 persons per year was reported recently in the US (1). It usually affects elderly people, and it is characterized by high level of blood monoclonal IgM, bone marrow involvement by lymphoplasmacytic lymphoma cells, insidious onset, and relatively benign clinical course with many patients diagnosed incidentally by routine blood examination. The most common symptoms are weakness, anorexia, and weight loss (2). Peripheral lymphadenopathies and hepatosplenomegaly may be present as well as ocular or central nervous symptoms (12). Among clinical features, pleural manifestations are uncommon (3,4,12,13). Indeed, Imhof et al summarized 114 cases of MW in 1959 with no mention of lung or pleural involvement (12). In 1974 Winterbauer et al reviewed 15 cases of pleuropulmonary involvement in MW reported in the English literature with 7 cases of pleural effusion (4). Rausch and Herion

reviewed 44 cases of pulmonary disease in the world literature from 1957 to 1979. Pleural effusion was evident in 19 cases (isolated pleural effusion in 4) (13). In 1973, Yamaguchi reviewed 54 Japanese cases and only 5 patients were found to have clinical pulmonary disease with 1 case of pleural effusion (14). In 1998 Fadil and Taylor reviewed 34 cases of pleuropulmonary involvement in WM patients reported in the English literature with 14 cases of pleural effusion (3). Based on these studies, chylothorax is a very uncommon presentation with only seven cases reported to date in literature (5-11).

Chylothorax usually results from the disruption and/or obstruction of the thoracic duct with consequent leak of chyle from the duct itself or one of its tributaries (15). Malignant obstruction of the thoracic duct is a major cause of non-traumatic chylothorax with lymphoma accounting for 70% of cases (16,17). Enlarged and/or confluent lymph nodes compress lymphatic channels as well as block the centripetal drainage of lymphatic flow through the thoracic duct. Collectively these events lead to diffuse extravasation or oozing of chyle and lymph into the pleural space.

In our case, mechanisms causing chylothorax remain unclear although the presence of chyle within the pleural cavity implies the involvement of the thoracic duct or one of its major tributaries. Remarkably, CT scan did not show thoraco-abdominal lymphadenopathy and the thoracic duct was not dilated (*Fig. 2*). Pleural biopsies showed a subpleural tissue infiltration of lymphoplasmacytic lymphoma cells. This pattern, previously described in WM patients without chylous pleural effusions, could lead to peripheral lymphatic channel compression and widespread leakage of lymph rather than chyle into the pleural space (18,19). Based on minimal thoracic duct leak detected with CT scan, involvement of the thoracic duct by lymphoplasmacytoid cells may be hypothesized with duct permeability modification.

The possible aggravating role played by chemotherapy in the occurrence of chylothorax is an issue of timely discussion with rituximab implicated. To date no published case of rituximab-related chylothorax has been reported, but chylothorax has been cited by the FDA as an uncommon side effect of such treatment.

Timing of pleural involvement represents a further issue which makes our case report unique. Since a chest CT scan was not performed before any treatment, it is difficult to know the exact time of pleural involvement. Due to the patient reporting onset of respiratory distress at the end of the first cycle of therapy, we assume that pleural involvement and chylothorax were already present at the time of diagnosis. However, as therapy resulted in decreased IgM levels and lymphoplasmacytoid cell counts in the bone marrow, failure of therapy for the pleural infiltrations should be considered. A similar case has been previously reported: a 77-year old woman with a non-chylous pleural effusion and biopsy proven pleural involvement of WMG was treated with Rituximab followed by fludarabine (19). Although the serum IgM dramatically decreased, her pleural effusion persisted and progressed. To explain this phenomenon, poor penetration of drugs into the pleural space or development of a resistant phenotype were hypothesized (19). By contrast, pleural involvement occurring after chemotherapy could be considered as an isolated pleural recurrence of the disease as previously reported (4,18,19).

CT performed after lymphangiography is reported to detect even small amounts of contrast material in the pleural space, confirming the chylous leak (20). Therefore, a chest CT scan was carried out in our patient, which showed, along with thoracic duct integrity and preserved flow, the presence of pleural flocculation that prompted us to speculate existence of minimal leak sites responsible for the observed chylothorax.

Whereas surgical therapy is often recommended when post-surgical chylothorax

occurs, typically a conservative approach represents the first choice option in case of a malignant etiology (15-17). Successful conservative treatment may be predicted according to results from lymphangiography. Indeed, duct patency, absence of leaks, or presence of minimal leaks in minor tributaries are positive prognostic markers for successful conservative treatment as well as drainage of less than 300 mL/day (15). In line with these data, a conservative approach based on fasting, parenteral nutrition, and octreotide was initially performed in our patient. Noteworthy, randomized animal studies support use of octreotide also in treating chylothorax caused by postoperative thoracic duct injury (21). Thus, somatostatin or octreotide have been previously used to reduce both intestinal chyle production and chyle leak (22-25). Similarly, in our patient such an approach resulted in improved nutritional status and clearer fluid; however, a steady leak rate of 500 mL daily was observed for a week.

As a consequence, we thought that a minimally invasive surgical approach was indicated in order to explore the pleural cavity, obtain a pleural biopsy, and finally to perform talc pleurodesis. The latter is a traditional option in malignant chylothoraces (26). A 100% success rate was reported in 19 patients with 24 chylothoraces secondary to lymphoma and refractory to chemotherapy or radiation therapy (27). The reported morbidity is low (26-28).

The main risk of chemical pleurodesis is producing a multiloculated chylothorax that can subsequently become organized. Talc slurry (administered via chest tube) distributes quite poorly over the pleural surfaces and tends to collect at the caudal sinuses (29). Thoracoscopic talc "poudrage" (insufflation via thoracoscopy) is reported to be at least equally effective, and in some studies significantly more effective than talc slurry (29,30). Indeed, a randomized trial that assigned 482 patients with malignant pleural effusions to receive talc insufflation or slurry

showed greater success at 30 days among patients receiving talc insufflation (78 versus 71 percent). In the subgroup of patients with primary lung or breast cancer, talc insufflation was significantly more successful at 30 days (82 versus 67 percent) (31).

Three hours before surgery, a fatty meal was administered to facilitate leak localization (32,33). If this had been identified, the use of fibrin glue or a lymphostatic patch or even ligation of the thoracic duct would have been considered. The pleural sinus was fully exposed by retracting the diaphragm inferiorly and the inferior pulmonary ligament was displayed. Since no macroscopic chylous leak or collections was evident, talc pleurodesis alone was considered to be adequate.

## CONCLUSIONS

Chylothorax represents an uncommon manifestation of WM with pleural involvement. It can be resistant to chemotherapy or can occur at the time of WM relapse. Mechanisms causing chylothorax are frequently unclear but CT scan associated with lymphangiography may be useful to investigate causes as well as to plan appropriate treatments. Thoracoscopic talc pleurodesis, in parallel with the use of glues or lymphostatic material, is recommended in case of failure of a conservative approach.

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