CASE REPORT

A rare case of bilateral chylothorax: a diagnostic challenge—follicular lymphoma versus primary effusion lymphoma

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SUMMARY

Chylothorax is most common on the left side owing to the position of the thoracic duct. Malignancy-associated chylothorax is not uncommon. However, bilateral chylothorax is rare and malignancy should be a consideration in absence of trauma. We report a case of a patient with follicular lymphoma who presented with bilateral pleural effusion; pleural fluid analysis confirmed chylothorax. The patient did not have any significant peripheral or axial lymphadenopathy, which made the diagnosis difficult in absence of histopathology. Pleural fluid analysis was negative for malignant cells, however, the flow cytometry markers were suggestive of follicular lymphoma. Primary effusion lymphoma, which could have been another possibility, was ruled out by the flow cytometry markers. We conclude that pleural fluid flow cytometry markers play an important role where there is no significant lymphadenopathy and in absence of histopathological diagnosis. This demands further evaluation.

BACKGROUND

Chylothorax has a wide range of aetiology.¹ Malignancy associated with chylothorax is not uncommon, but chylothorax as a presentation of malignancy is rare. Among malignancy-associated conditions, malignant lymphoma and bronchogenic carcinoma are the most common. Several case reports of chylothorax associated with Hodgkin's and non-Hodgkin's lymphomas (NHLs) have been described.^{2–6}

Follicular lymphoma is the most common clinically indolent NHL. Most patients with follicular lymphoma present with painless peripheral adenopathy in the cervical, axillary, inguinal and/or femoral regions. While hilar and mediastinal nodes are often involved, large mediastinal masses are rare. Pleural fluid cytology is usually negative for malignant cells in many of the cases and diagnosis is made by available lymph node biopsy.

Primary effusion lymphoma (PEL), formerly known as body cavity lymphoma, accounts for about 4% of all HIV-associated NHLs.⁷ PEL cells are morphologically variable with a null lymphocyte immunophenotype with evidence of human herpes virus (HHV) 8 infections.⁸ PEL cells typically display a 'null' lymphocyte phenotype, meaning that CD45 is expressed, but routine B-cell (including surface and cytoplasmic immunoglobulin, CD19, CD20, CD79a) and T-cell (CD3, CD4, CD8) markers are absent. Instead, various markers

of lymphocyte activation (CD30, CD38, CD71, human leucocyte antigen DR) and plasma cell differentiation (CD138) are usually displayed.

We describe a case of a patient who presented with bilateral pleural effusion, who was found to have chylothorax without any significant lymphadenopathy, which made it difficult to diagnose in absence of histopathology. Pleural fluid cytology was negative for malignant cells; however, the pleural fluid flow cytometry markers favoured the diagnosis of follicular lymphoma. The patient received chemotherapy resulting in improvement of pleural effusion.

CASE PRESENTATION

A 75-year-old African-American man was admitted to hospital with shortness of breath. He denied having any significant medical problems and was not taking any medications. He was in good health, but reported shortness of breath for the past 2–3 weeks before admission. He used to walk 4–5 blocks without any difficulty, but would now get short of breath walking less than a block. No limitation at rest and no chest pain or cough was reported. On review of his system, the patient did not have fever or chills, but admitted to weight loss of about 5–6 pounds in the last 1 month. He also admitted to poor appetite. He claimed to be a never smoker and non-drinker, and stated that he did not use illicit drugs.

On physical examination, the patient was haemodynamically stable and oxygen saturation was good. He had a normal body build with mild distress due to shortness of breath. He had two palpable lymph nodes on the right inguinal region that were 0.5–1 cm in length, soft and non-tender. Breath sounds decreased on bilateral lung base. Other physical findings were normal.

INVESTIGATIONS

Laboratory results showed white cell count (WCC) 8 K/μL, haemoglobin 12.2 g/dL, platelet count 214 K/μL, international normalised ratio 1.0, blood urea nitrogen 18 mg/dL, creatinine 0.9 mg/dL, total protein 5.6 g/dL, albumin 3 g/dL, with normal liver function test result. Chest X-ray showed bilateral pleural effusion, more on the right than left (figure 1).

The patient was admitted to the medicine floor with an impression of pneumonia versus malignancy. CT of the chest and thoracentesis with pleural fluid analysis was planned. CT of the chest

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Figure 1 X-ray of the chest on the day of admission, showing bilateral effusion.

reported a bilateral large pleural effusion, greater on the right, no parenchymal lesions and no mediastinal or axillary lymphadenopathy (figures 2 and 3). Under ascetic precaution, right thoracentesis was performed and 1600 mL of milky appearing (chylous) fluid drained. Fluid analysis revealed white cell count (WCC) of 1338 with 88% of lymphocytes and red blood count (RBC) of 15 525. On chemistry, glucose was 137 mg/dL, protein 4.4 g/dL, lactate dehydrogenase (LDH) 146 U/L, cholesterol 96 mg/dL and triglyceride was 826 mg/dL. Fluid pH was 7.46. Blood chemistry reported glucose of 106 mg/dL, total protein 5.9 g/dL and LDH 351 U/L. On the basis of the Lights criteria, fluid was exudative.

Fluid adenosine deaminase (ADA) level was also sent; it was mildly elevated at 26.8 (U/L). Reference normal value was <9.2. In reference laboratory ADA mean was 92.1 U/L in tuberculosis, mean 23.3 U/L in metastatic malignancies, 34.9 U/L in mesothelioma, mean 23.8 U/L in pulmonary embolism and mean 64.3 U/L in lymphoma. Tuberculosis was excluded, but raised the suspicion of malignancy. HIV status was unknown at presentation, however, tests came back negative and HHV-8 was not tested.

Pleural fluid cytology was negative for malignant cells; there were abundant reactive lymphoid cells, some polymorphonuclear leucocytes, a few scattered macrophages, mesothelial

cells and blood cells reported in pleural fluid. Pleural fluid analysis was non-conclusive. CT of the abdomen was ordered to look for an intra-abdominal source of malignancy (figure 4). The scan revealed normal liver and spleen size with small multiple simple 1.5–2 cm cysts in the liver, and a moderate amount of perihepatic and intra-abdominal ascites, with poorly defined porta hepatic nodes presented. There was also periaortic lymphadenopathy noted from coeliac axis aortic bifurcation. Subcentimetre iliac nodes were seen.

Pleural fluid flow cytometry markers were sent for testing. Lymphocytes were selected for analysis based on CD45 staining intensity with forward and side scatter. These were reported as predominantly small lymphocytes, with clonal CD20+ B cells detected, which co-expressed dim CD10 and κ light chain and were negative for CD5 and CD11c, comprising 22% of lymphocytes. Diagnostic consideration was given to follicular lymphoma.

On the basis of the clinical features and pleural fluid cytometry, a diagnosis of follicular lymphoma stage IV was made.

DIFFERENTIAL DIAGNOSIS

Pulmonary lymphangioleiomyomatosis is a rare lung disease that afflicts young women of childbearing age and may present with chylothorax. Our patient did not have any features of this rare disorder.

TREATMENT

In hospital, the patient started chemotherapy with a R-CHOP regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

OUTCOME AND FOLLOW-UP

The patient will receive the rest of the chemotherapy as an outpatient.

DISCUSSION

Chylothorax is caused by the disruption or obstruction of the thoracic duct or its tributaries, resulting in leakage of large amounts of chyle in the pleural space. Chylothorax is a rare cause of pleural effusion. Malignancy is the leading cause of non-traumatic chylothorax.¹ Lymphoma, chronic lymphocytic leukaemia and metastatic cancer have been reported as a cause of malignant chylothorax.¹ Both Hodgkin's and NHL

Figure 2 CT of the chest showing bilateral pleural effusion without any parenchymal lesion.

Figure 3 CT of the chest mediastinal view showing bilateral effusion with normal mediastinal structure.

Figure 4 CT of the abdomen showing a few hepatic cysts without any significant lymphadenopathy.

reportedly have an association with chylothorax. O'Callaghan *et al*⁹ published a case series of four patients of chylothorax with NHL. Two were diagnosed with follicular lymphoma and two had mixed follicular lymphoma with diffuse large B-cell lymphoma. All four patients were diagnosed by lymph node biopsy.

Follicular lymphoma is the second most common form of NHL and, in the USA, follicular lymphoma accounts for approximately 35% of NHLs and has an estimated incidence of 3.18 cases/100 000 people.¹⁰

Lymphoma is diagnosed by lymph node biopsy with specific immunohistochemical markers. However, patients without significant lymph node involvement make it difficult to diagnose. The question is, how reliable are flow cytometry markers in absence of a histopathological diagnosis? All published cases have a histological diagnosis. Our case was rare in the absence of significant lymphadenopathy, and was a diagnostic challenge.

PEL was a differential although it has been reported mostly in HIV-positive patients. PEL has a strong association with HHV-8. Our patient was HIV negative, but his HHV-8 status was unknown. The diagnosis of PEL is usually made on cytological preparation of the involved effusion fluid, but biopsies of body cavity-lining tissue may also show small numbers of neoplastic cells adherent to mesothelial-lined surfaces. Our patient did not fulfil the criteria of null lymphocyte immunophenotype of peripheral blood lymphocyte (PBL) cells. Again, the reviewed literature did not mention how common chylothorax in PEL is.

We diagnosed the case based on clinical findings with the aid of pleural fluid flow cytometry markers in the absence of

histopathology. We propose further evaluation of the role of pleural fluid flow cytometry markers in diagnosis of malignancy when tissue diagnosis is a challenge.

Learning points

- ▶ Non-traumatic chylothorax leads to malignancy.
- ▶ Bilateral chylothorax is a rare presentation of follicular lymphoma.
- ▶ Pleural fluid flow cytometry is an important tool in absence of significant lymphadenopathy for histopathological diagnosis.
- ▶ Primary effusion lymphoma is diagnosed by a null lymphocyte panel in flow cytometry.

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Competing interests None declared.

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