Mantle Cell Lymphoma Presenting With Persistent Pleural Effusion And Severe Thrombocytopenia
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Citation

Abstract
The differential diagnosis of pleural effusions is a common problem in everyday clinical practice. Usual tests that are been used to identify the causes of a pleural effusion are the type of cells, Light's criteria, microbiologic examinations, and cytological examinations of the pleural fluid. A number of other markers (such as adenodeaminase, interferon-γ, and vascular endothelial growth factor) have been found to differ between pleural effusions caused by different diseases. We report a case of a 69-year old patient who presented with a persistent lymphocytic pleural effusion and severe thrombocytopenia. The diagnosis after an extensive evaluation was mantle cell lymphoma of the pleura. The aforementioned markers in pleural fluid raised suspicions that led to the final diagnosis.

CASE HISTORY
A 69 year-old male farmer, non-smoker, was admited to our department due to dyspnea on exertion, night sweats during the last two months and severe thrombocytopenia revealed during a routine screening by his general practitioner. The patient had a medical history of congestive heart failure, and osteoarthritis.

Physical examination revealed body temperature 36.8°C, pulse rate 80 beats/min, blood pressure 150/90 mmHg, respiratory rate 20 breaths/min and oxygen saturation 94% on room air. Auscultation disclosed decreased breath sounds at the right lower base, with dullness on percussion. In addition the patient had ecchymoses in his lower limbs and trunk without petechiae. Laboratory work-up showed: hemoglobin 15.6 g/dL, white blood cell count 10,900 cells/µL (71% neutrophils and 18% lymphocytes), and platelet count 20,000 cells/µL. Prothrombin time and partial thromboplastine time where within normal limits, as well as the rest of the laboratory tests.

The patient's chest x-ray on admission (Figure 1 a and b), revealed a pleural effusion on the right hemithorax and a thoracentesis was performed. The pleural fluid was compatible with exudate (pleural fluid LDH 181 U/L, pleural fluid/serum LDH ratio 0.71, pleural fluid/serum protein ratio 0.68) with 91% lymphocytes, glucose 144 mg/dl, and pH 7.42. Computed Tomography (CT) scan of the chest is shown in Figure 2. The patient's tuberculin skin testing and three consecutive sputum and pleural fluid smears for M. tuberculosis were negative. Bone marrow smear showed an increased number of megakaryocytes which was combatible with immune mediated thrombocytopenia. All other causes of secondary thrombocytopenia were carefully excluded (e.g. systemic lupus erythematosus). By that time the patient had developed life-threatening thrombocytopenia and oral corticosteroids (1mg/kg/d prednisone) were started for the treatment of the immune-mediated thrombocytopenia with good response. Cytologic examination of multiple consecutive pleural fluid samples was not diagnostic.
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Figure 1
Figure 1ab: The patient’s chest x-ray on admission. A large pleural effusion can be seen on the right hemithorax.

Figure 3
Figure 3ab: CT scan of the chest revealed a right-side pleural effusion of the right hemithorax and protracheal and subcarinal mediastinal lymph nodes.

Due to the persistence of the pleural effusion he was subsequently submitted to video-assisted thoracoscopic surgery that was not diagnostic. A further panel of biochemical markers in the pleural fluid at that time included the following: adenodeaminase (ADA) 52.6 IU/L, interferon-γ (IFN-γ) 2.3 IU/ml, and vascular endothelial growth factor (VEGF) 828 pg/ml. The two biochemical markers that have been used for the diagnosis of tuberculous effusions had contradictory results in this patient. ADA value was indicative of tuberculosis, while IFN-γ levels were relatively low, being not suggestive of tuberculosis. Additionally, the high value of VEGF was suggestive of malignancy. Additional pleural fluid and sputum cultures for M. tuberculosis were negative.
These findings, along with the presence of immune-mediated thrombocytopenia and the persistence of the pleural effusion in the absence of a definite diagnosis led us to refer the patient for mediastinoscopy, two months after the withdrawal of oral corticosteroids and while he remained with normal platelet counts. The histological examination of a mediastinal pleura sample is shown in Figure 3 (a and b). The diagnosis was mantle cell lymphoma with pleural involvement and autoimmune thrombocytopenia.

**Figure 5**

Figure 3: Histology of the mediastinal pleura sample shown in revealed a monomorphic lymphoid infiltration with a diffuse growth pattern. The lymphoid cells are small to medium sized with irregular nuclear contours and scanty cytoplasm. The immunohistochemical hallmark of the neoplasm is shown in Figure 4, with a positive cyclin D1 stain in the nuclei of the lymphoid cells.

**DISCUSSION**

Pleural effusions appear in approximately 20% of patients with non-Hodgkin lymphomas (NHL), being in their majority lymphocytic exudates. The amount of fluid accumulated in lymphomas may vary and cause from little to severe respiratory symptoms. Malignant cells in pleural samples may be so spared that even experienced cytologists are unable to render a definite diagnosis. In this case several consecutive cytological examinations of the pleural fluid were not diagnostic.

Mantle cell lymphoma (MCL) represents approximately 5-10% of all cases of non-Hodgkin lymphomas. MCL tends to occur in middle-age to older people (median age, 60 years) and usually in males. The disease is commonly advanced during the presentation of clinical manifestations. Its features include generalized lymphadenopathy, along with bone marrow and liver involvement. About one half of patients have systemic symptoms (fever, night sweats and weight loss). Splenomegaly is present at initial diagnosis in almost 60% of the patients; however, that was not proven in the case of our patient. Other extranodal sites which are also frequently involved are the gastrointestinal tract, Waldeyer's ring and the nasopharynx, as well as the lungs and pleura. Mild anemia is also common at presentation, lymphocytosis occurs in 20-40%, whereas immune-mediated thrombocytopenia occurs in less than 15% of the patients.

MCL is a virgin B-cell lymphoma of the mantle zone or primary follicle lymphocytes. Immunohistochemically, the neoplastic cells are monoclonal B-cells (CD20 positive) and they are CD5 positive, bcl-2 positive, CD43 positive and cyclin D1 positive whereas they are CD10 negative, CD23 negative and bcl-6 negative. The immune profile helps in distinguishing this type of lymphoma from other small B-cell lymphomas. Approximately 50-65% of MCL cases exhibit the cytogenetic abnormality t(11;14)(q13;q32) which juxtaposes the bcl-1 oncogene on 11q13 with the IgH gene. The former has been shown to encode a cyclin designated cyclin D1, the overexpression of which is the hallmark for the diagnosis of MCL.

Immune-mediated thrombocytopenia is a common manifestation in lymphomas and usually is caused by autoimmune destruction of platelets. Diagnosis of immune destruction can usually be made from the clinical presentation and demonstration of an increase in marrow megakaryocyte number and ploidy. In the case of our patient the increased number of megakaryocytes in bone
marrow along with the absence of other causes of thrombocytopenia led us to the diagnosis of autoimmune thrombocytopenia, thus he was treated with oral corticosteroids with complete response. The use of corticosteroids might have been the reason for the non-diagnostic biopsy pleural samples taken during the video-assisted thoracoscopic surgery. The pleural involvement due to MCL was confirmed later as the final diagnosis was eventually established by a mediastinal pleural sample obtained with mediastinoscopy.

The biochemical markers at the time of the initial assessment of the patient were helpful in the further evaluation. High ADA levels in lymphocytic exudates (above 40 IU/L) are usually related with tuberculous pleural effusions. The combination of high ADA and IFN-γ values in the pleural fluid can lead to the diagnosis of tuberculosis with a great sensitivity and specificity. However, in the case of our patient, the IFN-γ levels on the pleural fluid were low, thus the diagnosis of tuberculosis was unlikely. Additionally, increased ADA values can be found in pleural effusions caused by hematologic malignancies and more rarely by other malignancies. Finally, the high VEGF levels were indicative of the malignant etiology of the effusion. An interesting aspect in the evaluation of this patient was that these three markers (ADA, IFN-γ and VEGF) in association with the presence of autoimmune thrombocytopenia were suggestive of a lymphocytic malignancy as the cause of the patient's pleural effusion, even at a time when the histopathological confirmation was not possible probably due to the use of corticosteroids.

The overall prognosis for patients with MCL is generally poor. The clinical features that predict for a poor prognosis in MCL are generally the same as those found in other types of NHL. It has been reported that the presence of advanced stage disease, B symptoms, a poor performance status and bone marrow involvement are clinical predictors of survival. The patient received chemotherapy and radiotherapy and 6 months later he is clinically stable, while the pleural effusion and the mediastinal lymph nodes have disappeared.

References
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