

Pleural effusion and Waldenström macroglobulinemia: if cytology and flow cytometric findings do not match. A case report

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Abstract

Pleural effusion is a rare complication of lymphoplasmacytic lymphoma. When it occurs, traditional investigation techniques may not always be successful. Flow cytometry is a fast and precise diagnostic technique that can be helpful in the diagnosis of pleural localization of hematological diseases. We present a case report of

pleural localization of Waldenström macroglobulinemia detected by flow cytometry.

Case Report

A 79-year-old man suffering from Waldenström macroglobulinemia (WM) was admitted to the hospital because of fever, vomiting, and diarrhea for about 3 days. His medical history included arterial hypertension and a third-degree atrioventricular block (permanent pacemaker implanted in 2019). A chest X-ray at the emergency room showed pulmonary infiltration on the right basis (Figure 1A). The blood analysis revealed signs of hypochromic anemia (hemoglobin 8.7 mg/dL, mean corpuscular hemoglobin 25.3 pg), C-reactive protein (CRP) 9.42 mg/dL, and white blood cells in the normal range. After 2 weeks, the patient developed a bilateral pleural effusion (Figure 1B), fever, and an increase in CRP. The patient was referred to our practice to perform a pneumatological examination for the suspicion of pulmonary/pleural infection. The chest ultrasound showed bilateral pleural effusion occupying about three intercostal spaces. We performed a right diagnostic and therapeutic thoracentesis with drainage of 1400 mL of fluid. Microbiological tests were negative. The cytological examination showed regular mesothelial isolated cells, histiocytes, and granulocytes. Pleural fluid resulted as a transudate with mononuclear cells 214/ μ L [protein 2 g/dL, pleural fluid/serum protein ratio 0.32, pleural fluid/serum lactate dehydrogenase (LDH) ratio 0.54, serum LDH 185/UL, fluid LDH 100/UL]. We also sent a sample of pleural fluid to the laboratory of hematology to perform an immunophenotyping with monoclonal antibodies. The results showed CD45+/CD19+/SmIg-kappa+: 0.00%, CD45+/CD19+/SmIg-lambda+: 0.00%, CD45+/CD19+/CyIg-kappa+: 10.24%, CD45+/CD19+/CyIg-lambda+: 0.00%, CD45+/CD5+: 14.11%, numerous erythrocytes and nucleated cells, of which approximately 62% were monocytes/macrophages, 30% lymphocytes, 6% neutrophils and 2% mesenchymal cells. Flow cytometry showed about 10% monoclonal B cells. In conclusion, the findings were compatible with malignant pleural effusion by the known lymphoplasmacytic lymphoma.

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Discussion

WM is a low-grade B-cell lymphoproliferative disorder characterized by bone marrow infiltration by lymphoplasmacytic cells associated with a monoclonal immunoglobulin M protein in the serum. The typical clinical features of WM are anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and rarely hyperviscosity. Pulmonary and pleural involvement due to WM is rather rare, only occurring in 3-5% of all extramedullary

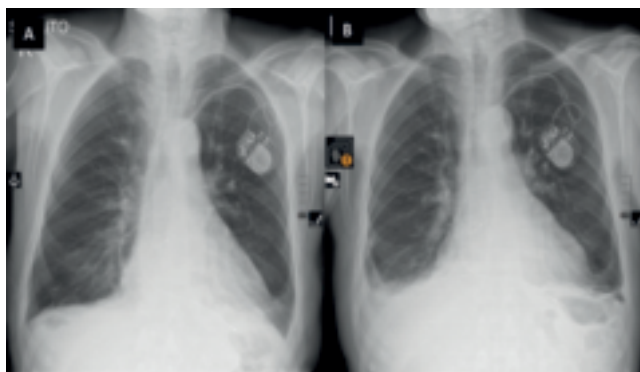


Figure 1. A) Chest X-ray on admission; B) chest X-ray after 2 weeks.

cases [1]. Extramedullary WM is characterized by the presence of clonal lymphoplasmacytic infiltrate in distant sites from the bone marrow or contiguous soft tissue in a patient with known WM, excluding splenic/liver and nodal involvement and circulating tumor cells. Banwait *et al.* described a longitudinal cohort of 985 patients with WM. Many of these cases showed involvement in specific organs such as the lung, soft tissue, central nervous system, and gut. According to the authors, it could suggest a possible specific tropism of the clonal cells to those organs. Pulmonary involvement was found in 13 patients (1.32%). In those 13 patients, the median time to the extramedullary pulmonary presentation was 6 years after diagnosis, and 10/13 patients had pleural effusions [2]. Extramedullary involvement in WM also appears more prevalent among patients with advanced disease or in those previously treated. This may be due to the selection of a clone with extramedullary preference in reaction to therapeutic influence. In agreement with the thesis, Banwait *et al.* and Gustine *et al.* assumed that this clonal evolution could explain the incidence of pleural effusions described in nine patients with WM, as it occurred after multiple therapies and about 10 years after the initial diagnosis [2,3].

Although our patient had a fever and increased inflammation markers, the origin of the pleural effusion was not clear. The etiology of idiopathic lymphocytic pleural effusion involves numerous conditions, including neoplastic and non-neoplastic diseases. Pleural biopsy can be useful but may be non-diagnostic in a significant number of cases if there is no pleural involvement or due to sampling errors [4].

The cytological examination is the most used method to study cells in the pleural fluid; however, it might be very difficult to recognize and distinguish abnormal plasma cells in pleural fluid due to varying morphology, particularly in the pauci-cellular samples [5]. In this case, flow cytometry could be helpful in determining whether the known WM was the underlying cause of the pleural effusion. Because of the limited number of malignant plasma cells and their potential *in vitro* degeneration, diagnosis may fail in patients undergoing pleural effusion puncture examination [6]. In our case, the cytological examination of pleural fluid was negative, also because the pleural fluid was poor of cells and they did not show malignancy characteristics. Immunophenotyping is a technique coupling specific antibodies to fluorescent compounds to measure specific protein expression within a cell population. The

protein expression is used to identify and categorize the tagged cells. The ability of flow cytometry to determine the presence or absence of cell-surface markers serves as the basis of immunophenotyping [7]. Flow cytometry is widely used in the diagnosis, identification, disease monitoring, evaluation of efficacy, and prognosis in various fields, such as hematology, immunology, oncology, and genetics. Flow cytometry gained increasing importance in the diagnosis and prognostication of hematological diseases. However, it is not widely used in the diagnosis of pleural effusion. Flow cytometry is a potentially useful diagnostic tool for clinical practice. Its advantages include the possibility to distinguish between normal, reactive, and malignant plasma cells. It can be used in the evaluation of body fluids, such as pleural fluid, too [8]. Flow cytometry immunophenotyping can separate the reactive cells from the malignant due to their aberrant antigen expression. Neoplastic plasma cells display aberrant phenotypes and restricted immunoglobulin light chain expression at the cytoplasmic and sometimes at the surface membrane level. The aberrant plasma cell phenotype includes underexpression of markers like CD19, CD38, CD45, CD27, and CD81 and overexpression of CD56, CD20, CD117, CD28, and CD200 [5].

Conclusions

Pleural effusion is a rare complication of WM. Flow cytometry is fast and accurate, and it has objective characteristics in the identification and analysis of cells. In addition, flow cytometry can be used as an adjunct diagnostic technique when the pleural localization of hematological disease is suspected.

In conclusion, this case demonstrated that flow cytometry is a useful complement to traditional diagnostic methods of pleural effusion.

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