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Monoclonal gammapathy of undetermined significance progression to Waldenstrom Macroglobulinemia with a pleural infiltration

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Abstract

Waldenstrom's Macroglobulinemia is a disease included in the lymphoproliferative syndromes. The pleural affectation is rare and its diagnosis supposes a challenge, due to the several differential diagnoses that can simulate the same symptoms.

The authors present a clinical report of the progression of a Monoclonal gammopathy of undetermined significance to Waldenstrom's Macroglobulinemia, coexisting with a pleural effusion secondary to the progression of the hematologic disease. To refer that the particularity of this case focusing on the importance of performing a biopsy but also to integrate the findings of serum and pleural fluid electrophoresis, findings that confirm the diagnosis.

Keywords

waldenstrom macroglobulinemia; pleural effusion; monoclonal gammapathy of undetermined significance (MGUS)

Introduction

Waldenstrom's Macroglobulinemia (WM) is a monoclonal proliferation of B-cells, located in the bone marrow and in the lymphoid organs. This proliferation of lymphocytes has the capacity to generate a large amount of monoclonal immunoglobulin M [1,2].

Compared with other lymphoproliferative syndromes WM is considered a rare entity, with a low reported incidence, 0.3 cases per 100,000 people per year [3]. Pleural effusion, as a clinical manifestation of a pleural affectation due to WM, is also an infrequent syndrome [1] with a reported incidence between 0-3% in some series of cases [4,5].

We present the case of a patient with a past history of a Monoclonal Gammapathy of Undetermined Significance (MGUS) hospitalized to study a pleural effusion, where the transformation to WM with a pleural infiltration was evidenced.

Case Report

81-year-old male with a history of hypertension and MGUS, who does not take any medication, was admitted to the Emergency Department, due to an acute right chest pain that radiated to the

the ipsilateral dorsal region, worsening with deep inspiration and associated with dyspnea.

The physical examination revealed: Tachycardia of 101 beats per minute, tachypnea with a saturation of 91%. In the lungs auscultation, there was a decreased of the vesicular murmur in the lower third of the right lung (stony dull on percussion in the same area) with bilateral crackles; without other relevant findings.

Initially, the arterial gasometry (FiO_2 32% by nasal cannula) and the laboratory data reveled: pH 7.481, pCO_2 31.1 mmHg, pO_2 105 mmHg, HCO_3^- 24.4 mEq/L, saturation 99%, lactate 1,8 mmol/L, hemoglobin 8.2 g/dL, mean corpuscular volumen 93.8 fL, mean corpuscular hemoglobin 30.1 pg, 6,100/L leukocytes 75.3% neutrophils, 102,000 platelets, creatinine 1.9 mg/dL, urea 64.5 mg/dL, glicemia 141 mg/dL, LDH 317 U/L and CRP 9.96 mg/dL. A Chest X-ray was performed and a massive pleural effusion on the right hemithorax was confirmed (Figure 1).

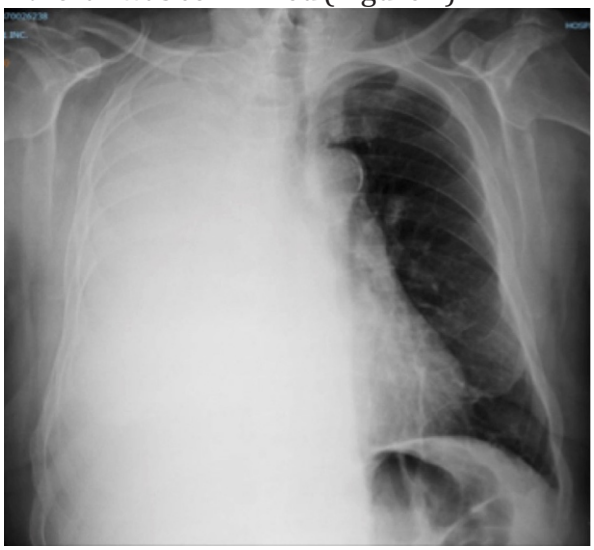

Figure 1: Chest X-Ray. Massive pleural effusion on the right hemithorax.

The patient underwent to a diagnostic and therapeutic thoracentesis, with symptomatic relief of the pain and the dyspnea. The pleural fluid examination showed a serohematic fluid with 6,748 cells/mm^3 and 75.3% of mononuclear cells, pH 7.9, proteins 5.2 g/dL, albumin 2.3 g/dL, glucose 29 mg/dL, LDH 3222 UI/L, amylase 35 U/L, compatible with an exudate.

After pleural fluid and blood cultures were taken, empiric Ceftriaxone was started, thinking in a parapneumonic effusion. The patient was admitted in the Internal Medicine Department.

Inicially, the patient maintained the dyspnea (needing several toracentesis), the oxygen requirements (FiO_2 32% by nasal cannula) and the inflammatory laboratory parameters. All the cultures (blood and pleural fluid) were negative.

As having a effusion recurrent, furthermore biochemical analysis of pleural fluid were performed to better characterize the exudate and see the progression: Adenosine Deaminase > 101 U/L, LDH 2877 U/L and glucose <5 mg/dL; additionally a pleural biopsy was performed to discart tuberculosis or malignancy as the ethiology. The anatomopathological study of the pleural biopsy showed a dense chronic inflammatory infiltrate with non-necrotizing granulomas.

In view of the obtained results, the Pneumology team were requested for the placement of a thoracic drainage tuve (Figure 2) to control the symptoms and allowed to perform a Computerized Axial

Tomography of the thorax, which did not showed significant parenchymal or pleural alterations, just a hydropneumothorax and a subcutaneous emphysema on the right lateral chest wall due to the drainage procedure (Figure 3).

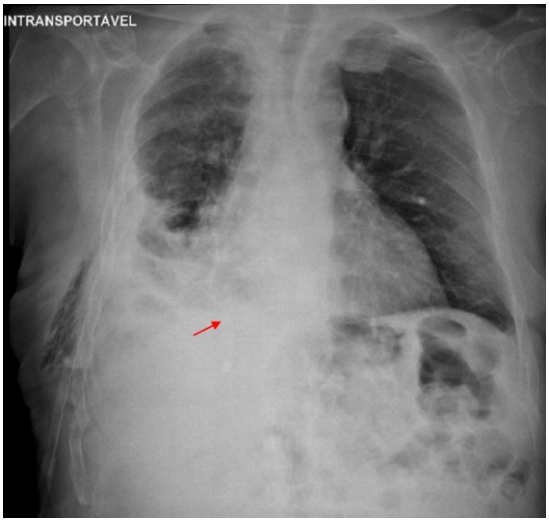

Figure 2: Chest X-ray. After placement of a chest tube (arrow) where there is pleural effusion in the lower 1/3 of the right lung.

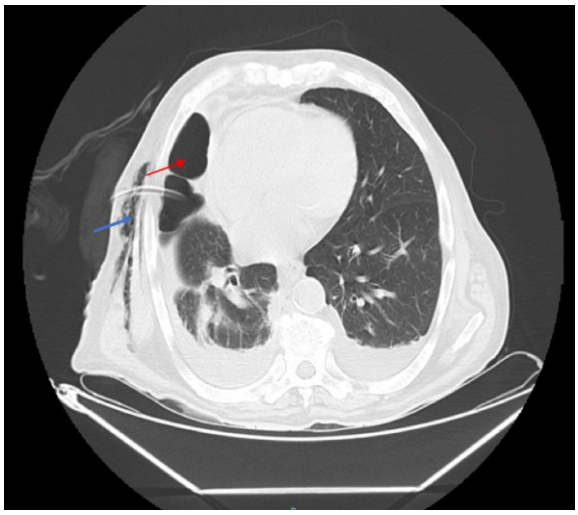

Figure 3: Thoracic CT-scan. Bilateral pleural effusion with an hydropneumothorax (red arrow) in the right side and a subcutaneous emphysema (blue arrow) on the right lateral chest wall. Slight deviation of the mediastinum.

The culture of pleural biopsy, including the search of mycobacterium and Acid-Alcohol Resistant Bacillus were negative.

At this point, as possible differential diagnosis were considered: Tuberculosis, granulomatous diseases and neoplastic processes; it was decided to continue with additional laboratory tests that would allow us to assure with some certainty the diagnosis. We highlighting the following: Beta 2-microglobulin 8366 g/L, serum protein electrophoresis with hypergammaglobulinemia (Figure 4), serum immunoglobulins (IgG 1174 mg/dL, IgA 104 mg/dL, IgM 1723 mg/dL), Interferon-Gamma Release Assays (IGRA) negative and serum Angiotensin-Converting Enzime (ACE) between normal value.

Electrophoresis of the pleural fluid showed the same monoclonal peak in the gamma region (figure 5), IgG 778 mg/dL, IgA 60 mg/dL and IgM 501mg/dL, as in the serum electrophoresis, orienting the diagnosis towards a probable malignant etiology.

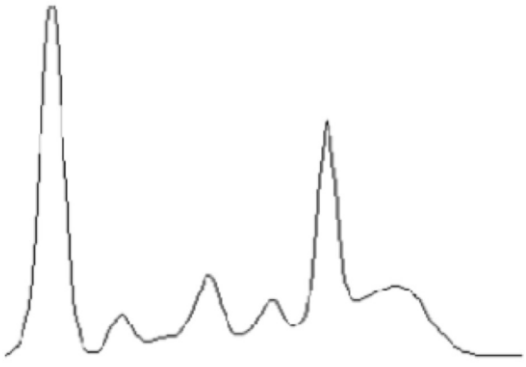

Figure 4: Serum protein electrophoresis. Hypergammaglobulinemia.

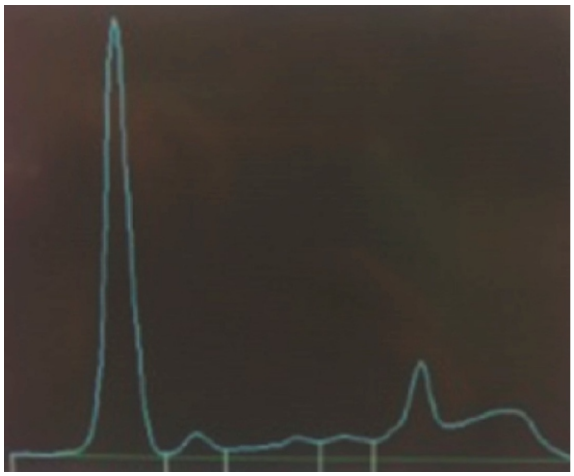

Figure 5: Electrophoresis of the pleural fluid. Monoclonal peak in the gamma region.

Pleurodesis was performed to control pleural effusion. The histopathology report of the pleural biopsy showed: A pleural infiltration by non-Hodgkin lymphoma B, CD20+ with the following Immunohistochemistry profile: CD20+, bcl-2+ and negative for: CD3, CD5, CD21, CD23, CD23, CD43, bcl-1 and cyclin D1; morphological suggestive of lymphoplasmocytic lymphoma (Figure 6).

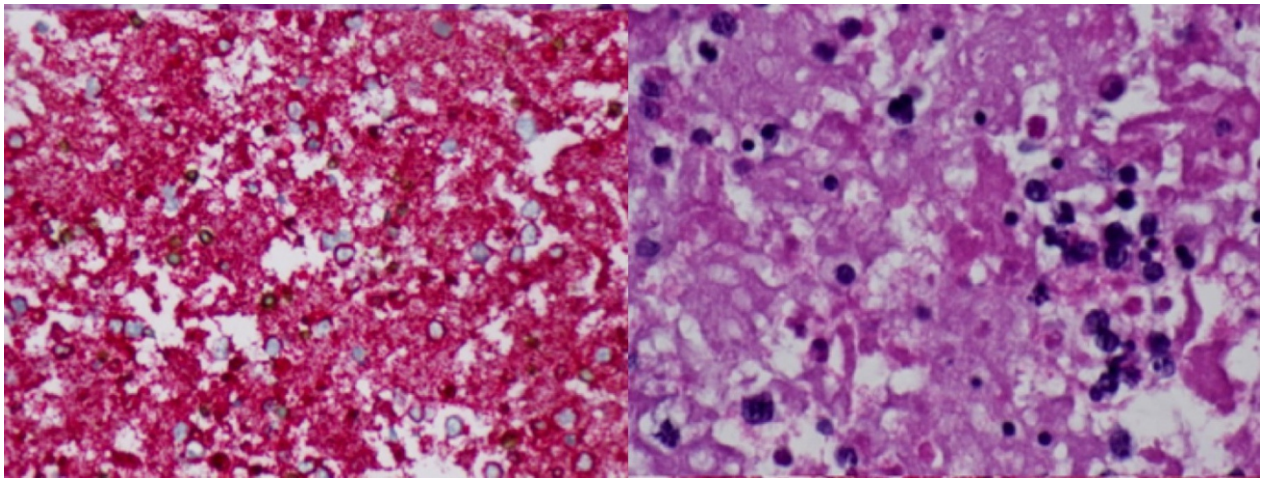

Figure 6: Pleural biopsy. Pleural infiltration by non-Hodgkin lymphoma B, CD20 +. Hematoxylin and Eosin staining (40x10) (upper). Immunohistochemistry CD 20/CD3+ (40x10) (down)

The diagnosis of a MGUS transformation into WM with pleural infiltration was assumed and Rituximab was started to control the symptoms. After 6 months the patient remains asymptomatic under the established therapy.

Discussion

WM is a relatively rare disease, described by Waldenström in 1944 that is included in the lymphoproliferative syndromes [3]. The definition has undergone several modifications throughout history, since it is a nosological entity that is very difficult to clarify. It shares common characteristics with other lymphoproliferative syndromes, which makes it more difficult to diagnose, especially if it has an IgM monoclonal component associated [6].

In WM with pleural involvement, the most frequent symptoms are dyspnea followed by non-productive cough [4]. Pleuropulmonary involvement is exceptional, being the unilateral pleural effusion, the most infrequent clinical finding described [4,5]. The existence of a pleural effusion without other type of pulmonary involvement is even more infrequent, especially if it is not accompanied by other serositis (ascites or pericarditis). In the necropsy of WM patients, pleuropulmonary affectation was evidenced, despite not being described clinical manifestations [3].

The most described radiological patterns of pleuropulmonary involvement by WM are: Bilateral reticulonodular infiltrates, single masses, hilar/mediastinal adenopathies or pleural effusion, generally unilateral [4].

In the study of a WM and pleural effusion we should discard as differential diagnosis: congestive heart failure, bacterial / fungal infection, tuberculosis [7] or neoplasia [3].

The pleural fluid is usually serous or haematic [4] and has exudative characteristics. The study that most guided us in the case we presented was the agreement between the electrophoresis of the serum proteins and those of the pleural fluid, where the presence of a monoclonal band was evident in

both samples [4].

For the definitive diagnosis, the gold standard is the pleural biopsy, which must show a lymphocytic infiltration, and the appearance of granulomas without necrosis is also frequent. The latter make it necessary to rule out other diagnoses such as granulomatous diseases and tuberculosis (take into account that the biopsy of a tuberculosis may show granulomas with or without necrosis [8]. In the case we report, the greatest difficulty was to exclude the diagnosis of tuberculosis (endemic in our area), remember that in the first approach, the pleural fluid showed a low glucose and a high ADA and there was evidence of granulomas in the biopsy [9].

There are some studies that have shown, that pleural involvement in WM patients, can be diagnosis by using a flow cytometry of the pleural fluid [5,10]. The pleural biopsy could be useful, but it is described that in a significant number of cases it can be inconclusive, due to a not involvement of the biopsied pleural area or due to a not involvement of the pleural by the disease. In these tough situations, flow cytometry combinated with the cytological and the gene rearrangement analysis, can suggest an underlying lymphoproliferative disease [10].

The anatomopathological study of the disease is not pathognomonic and may mimic other interstitial pneumopathies. However, the sum of the clinical correlation, radiological, laboratory (mainly the agreement in the electrophoresis of the serum proteins and the pleural fluid) and histopathological data, is usually enough to define the diagnosis [11].

WM is currently a non curable disease with available treatments [12]. The treatment is focused on symptom control and prevention of organ damage. As all WM cells express CD-20, it is generally agreed that first-line therapy should consist of using an anti-CD20 monoclonal antibody, as rituximab, alone or preferably in combination with Bortezomib [12].

The evolution of MGUS to WM remains unclear, to simplifying these two entities, the distinction between MGUS and WM should be the existence of clinical manifestations [13].

In conclusion, we report the progression of a lymphoproliferative disease, presented with a unilateral pleural effusion, where the differential diagnosis included granulomatous diseases, tuberculosis and finally was diagnosed: A pleural involvement due to the underlying disease. For the diagnostic confirmation the electrophoresis of serum and pleural fluid proteins was used, as well as the demonstration of biopsy infiltration.

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