



Pleural Nodules and Effusion as a First Sign of Multiple Myeloma: A Diagnostic Challenge. A Case Report and Literature Review on the Incidence, Mechanisms of Extramedullary Spread and Treatment Options of Extramedullary and Pleura I MM

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Abstract

Approximately 6% of all patients with MM develop pleural effusion. Pleural effusions in MM are generally benign and due to conditions such as infections, hypoalbuminemia or congestive heart disease. Clinicopathological studies have revealed that the spleen, liver and lymph nodes are the most common sites of extramedullary disease with myelomatous pleural involvement resulting in less than 1% of all cases. We herein report about a 52 year old woman presenting to the Emergency Department of a tertiary care hospital with a lower back pain. We diagnosed a MM with a lambda light chain restriction presenting with multiple pleural nodules and pleural effusion as the first sign of the disease. The diagnose was made via semi rigid thoracoscopy and has been challenging since pleural involvement is a very rare manifestation of the disease, being even more rare as a first sign of it. Nevertheless physicians should be aware of the possibility of myelomatous pleural involvement both for prognostic and diagnostic reasons. We will report our case and review the general incidence, mechanisms of spread and treatment options of extramedullary disease. Finally we reviewed the literature on the association between MM and pleural involvement.

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Introduction

Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. Recent statistics from the American Cancer Society indicate that the incidence of MM is increasing; the annual incidence is around 4 per 100,000. The mean age of affected individuals is 62 years for men and 61 years for women [1]. Bone pain, particularly in the back or chest, is present at the time of diagnosis in more than two thirds of patients. Weakness and fatigue are common and are often associated with anemia. Fever is rare and, when present, is generally from an infection. Other symptoms may result from hypercalcemia, nephrotic syndrome, renal insufficiency, neuropathy or amyloidosis. Myelomatous pleural effusion is an uncommon manifestation, with only a few cases reported to date. Patients with myelomatous pleural effusion often have advanced-stage disease and poor prognosis; despite aggressive treatment [2]. We herewith present a challenging case of myelomatous pleural involvement as a first sign of the disease diagnosed with semi-rigid thoracoscopy.

Case Presentation

A 52-year-old woman presented to the emergency department of a tertiary care hospital with a dull lower back pain. She had suffered from kidney stones and metrorragy before and she had been hospitalized three weeks before for an episode of presyncope due to anemia. During that hospitalization a colonoscopy and a gastroscopy were performed excluding gastrointestinal bleeding; the ultrasound of the lower abdomen had shown a thickening of the endometrial wall for which the patient had been prescribed a hysteroscopy which she hadn't performed yet. On physical examination she was alert, awake and oriented. Pulse was rhythmic, blood pressure was 130/70, and SaO₂ was 96% without oxygen supply. She had no fever. On physical examination breathsounds were diminished at

the basis of the right lung. The abdomen showed normoactive bowel sounds and no guarding, no rebound, and no hepatosplenomegaly. Giordano sign was positive on the left costovertebral angle. She showed no deficits on neurological examination. Abdominal ultrasound showed mild splenomegaly and no signs of kidney stones or urinary tract infection. Urine tests were also negative for signs of infection. Chest X-ray revealed multiple nodules on the base of the right lung and an associated pleural effusion. Blood tests showed a normal white blood cells count, platelets were 91.000 per mm³ and microcytic hypochromic anemia with hemoglobin 7.3 g/dl for which the patient received a blood transfusion. Because of the presence of headache associated to anemia with high LDH level and low aptoglobin levels a blood smear was performed which didn't show any schistocytes but showed anisopoikilocytosis. The Quantiferon test and HIV test were negative, ANA antibodies were negative. The patient had positive HbsAg, HCV IgG were also negative. A chest and abdominal CT was performed showing multiple nodular pleural thickenings on the basis of the right lung and a large pleural effusion. CT also showed areas of bone rarefaction in the pelvis and sternum and a thickening of the posterior uterus wall. The diagnostic workup for MM was started including: Creatinine and BUN, serum calcium, LDH, beta2 microglobulin.

Evaluation of 24-hr urine for total protein and BJ detection. Serum analysis also included quantitative immunoglobulin levels, serum protein electrophoresis and serum immunofixation electrophoresis and a serum free light chain assay. Serum protein electrophoresis and immunofixation detected the presence of a lambda light chain monoclonal protein (15.100 mg/L) and a hypogammaglobulinemia. Evaluation of 24-hr urine showed a total proteinuria of 10g/24 hrs, BJ proteinuria was positive showing a quantitative proteinuria of 15g/24 hrs. Beta2 microglobulin was 4.7 mg/L and LDH was 336 U/L. Calcium levels and serum creatinine was normal. A bone marrow biopsy was performed showing clonal bone marrow plasma cells of 90% with a lambda light chain restriction confirming the diagnose of MM.

The MR of the spine showed diffuse low intensity marrow signal compatible with bone marrow reconversion and a disc herniation at the level of L3-L4. To best stage the disease and assess its activity the patient also underwent a PET with 18F-FDG which revealed areas of intense uptake in the left and right humerus, in the spleen, in the basis of the right lung and in the uterus corresponding to the area first seen on CT. To diagnose the origin of the pleural lesions a thoracoscopy was performed showing multiple lobulated hypervascularized yellow nodules on the right parietal pleura which were biopsied and a chest drain was placed to drain the pleural effusion. The cytological and mycobiological tests on the fluid were negative whereas the biopsy was positive for myelomatous tissue showing clonal plasma cells with a lambda light chain restriction and a ki-67 proliferation index of 50%. The patient also underwent transvaginal ultrasound; the biopsy performed on the uterine lesion showed endometrial hyperplasia.

Discussion and Conclusion

The case we reported has been a diagnostic challenge both because of the rarity of myelomatous pleural involvement and because of the coexisting endometrial lesions and history of metrorragy which could have explained the anemia of the patient. The suspicion of MM was first raised after the CT showed areas of bone rarefaction in the sternum and the pelvis associated with anemia.

Extramedullary spread in MM can present as PC leukemia or soft tissue plasmacytomas which can arise from either direct extension from focal bone involvement, hematogenous spread or triggered by invasive surgical procedures. Data on Extramedullary Disease (EMD) in MM are observational and, to date, no control studies are available. The incidence of EMD in patients with newly diagnosed MM ranges from 7% to 18% [3-6].

An additional 6% to 20% of patients develop plasmacytomas later in the course of the disease [3-6]. In two studies by Bladè et al., [3] EM involvement was reported in 15% to 20% of patients at diagnosis and in an additional 15% during follow up. The first of these studies was focused on 53 patients with IgD MM, a subtype known to be associated with a higher frequency of EM disease [3]. The second study focuses on 72 patients aged <40 years, another subset with high incidence of EM involvement [4]. Also in the series by Varettoni et al., [6] the median age of patients with EM disease was lower as compared with the rest of the MM population. This study has shown a statistically significant increase of EM involvement in more recent years, both at diagnosis and follows up. Both the widespread use of more sensitive imaging techniques and the improvement of survival due to the introduction of novel agents such as thalidomide, bortezomib and lenalidomide may at least partially explain this finding. Interestingly some authors reported high incidence of EM relapses after autologous or allogenic SCT. In a study of the Spanish Registry, 14% of patients relapsing after autologous SCT had EM manifestations, with minimal or absent monoclonal protein, indicating the existence of sanctuary sites not reached by intensive chemotherapy. In the series by Varettoni et al., [6] which analyzed 1003 MM patients over three periods of time (1971-1993, conventional-dose chemotherapy; 1994-1999, HDT for younger patients; and 2000-2007, introduction of novel agents), the incidence of EM relapses was not increased in patients receiving HDT as compared with other treatments [6], partially disproving the hypothesis advanced by Perez-Simon et al., [7] that the graft versus myeloma effect may control bone marrow disease, while plasma cells outside the bone marrow may escape immune control [7]. In Varettoni's study the only risk factor for EM recurrence was the presence of EMD at diagnosis, indicating that inherent biological characteristics of the disease rather than treatment are responsible for EM spread [6]. In a more recent review by Bladè et al. bone marrow genetic abnormalities were not associated with extramedullary spread per se; instead changes in the bone marrow microenvironment seem to be key for the development of extramedullary disease. Possible mechanisms include downregulation of chemokine receptors (such as CCR1, CCR2, CXCR 4), increased angiogenesis (through upregulation of VEGF and MMP-9) and decreased expression of adhesion molecules (VLA-4, P-selectin, CD44) [8]. EM Plasmacells tend to have a plasmablastic morphology; also a shift in secretion from intact Ig to free light chain (called light chain escape) has been described [9]. In a study by Ping Wu et al., [5] focusing on 459 patients with newly diagnosed symptomatic myeloma the presence of an EM disease was associated with higher hemoglobin, albumin, and lower B2-M level and consequently a more favourable ISS staging at diagnosis. However this finding could be explained by the early presentation of these patients caused by the tumors. The EM group also had fewer IgG heavy chain isotypes (36% vs. 61.2%, p<0.001), more Bence-Jones (30.7% vs. 13.8%, p<0.001) and non secretory (9.3% vs. 4.4%, p<0.09) types, as well as higher percentage of Lambda light chain isotypes (47% vs. 35%, p<0.05) Varettoni et al., [6] evidenced how the presence of EM involvement at any time during

the course of the disease was associated with shorter progression free and overall survival [6]. Ping Wu et al., [5] demonstrated that EM disease was associated with poorer prognosis in patients treated with conventional therapy [5]. In both studies patients with and without EMD who received high dose treatment had similar outcomes, indicating that high dose therapy can overcome the negative impact of EMD [5,6]. Concerning the use of novel agents, some reports indicate low efficacy of thalidomide on EMD, even in patients with good serological and marrow response, indicating that the molecule might need the bone marrow microenvironment to be effective. Bortezomib on the other hand seems more promising in this setting. At the best of our knowledge though, there are no studies focusing on the treatment of MM with EMD. Although the introduction of proteasome inhibitor and immunomodulators has improved the outcome and treatment of MM, studies to define the best therapeutic strategy for EM MM are still needed. Experimental and molecular studies on the mechanisms of interaction between myeloma cells and bone marrow microenvironment and the characteristics of myeloma cells at extramedullary sites could provide a great opportunity for new drug development in this setting.

Nearly all hematologic malignancies can occasionally present with or develop pleural effusions during the course of disease. The most common disorders are Hodgkin and non-Hodgkin lymphomas, with a frequency of 20% to 30%, especially if mediastinal involvement is present. Acute and chronic leukemias and myelodysplastic syndromes are rarely accompanied by pleural involvement. Pleural myelomatous involvement is even more rare [14]. Myelomatous pleural effusion is an uncommon manifestation. Approximately 6% of patients with MM develop pleural effusion. Pleural effusions in MM are generally benign and due to congestive heart disease, chronic renal failure, hypoalbuminemia, cardiac amyloidosis, pulmonary infarctions or infections. According to the literature available Myelomatous Pleural Effusion (MPE) results in less than 1% of all cases [15]. Few studies reporting the incidence of pleural involvement in MM have been conducted. Usmani et al., [16] reported a series of 1965 cases of MM. PET scans were performed to check for extramedullary involvement. The percentage of patients with pleural involvement at diagnosis was 3%, while another 6% showed pleural disease at the time of relapse. Young-Uk Cho et al., [17] summarized 734 cases of MM: 54 cases (accounting for 7%) had pleural effusion. Among them 42 patients had complete data. Myeloma cells were found in the pleural liquid by pathological examination in 19 patients. The other twenty three had benign pleural effusion.

MPE occurs due to direct extension of the plasma cells from adjacent chest wall lesions or pulmonary lesions, hematogenous spread, or due to lymphatic obstruction. Left sided MPE is more common than right side involvement and it tends to be associated more with IgA MM [18].

MPE is associated with poor prognosis and should alert clinicians towards the aggressive nature of the underlying myeloma. Our patient had a DSS stage IIIA and ISS stage II with tumor cells having a high proliferation rate as shown by the ki-67 index of 50%. Chemotherapy is the main therapy for pleural myeloma, despite the low response rate and short survival time. Because the incidence of MPE is low, very little is known about the diagnose of the disease. According to the literature available, routine pleural effusion pathological examination has shown to have low sensitivity, which was confirmed also in our case. Flow cytometry may therefore be a useful tool to improve the detection rate of myelomatous pleural effusion even if it is not

widely used as a routine diagnostic exam in the diagnosis of pleural effusions. According to our experience, semi-rigid thoracoscopy has shown to be a safe and effective method for obtaining pleural specimens for histopathological evaluation.

In conclusion we have described a complex case of pleural involvement as a first presentation of MM. In the differential diagnosis of malignant pleural effusion, physicians should not only consider primary malignant tumors in the chest or metastasis of systemic solid tumors but also hematological malignancies. It is also important to diagnose MPE in patients with MM especially because of its prognostic impact with it being associated with a poor prognostic outcome and a low response to treatment. It should be kept in mind that routine pathological examination of pleural effusion has a low sensitivity leading to false negatives and that flow cytometry can represent an important tool to raise the detection rate.

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