Malignant pleural effusion in multiple myeloma: a case report

Derrame pleural malign em mieloma múltiplo: relato de caso

Júlia Plentz Portich[1], Ebellins Tabares Calvache[1], Aline Sinhorelo Ribeiro[1], Vitor Barreto Santana[2], Cristiane Seganfredo Weber[1], Alessandra Aparecida Paz[1]

ABSTRACT

Multiple myeloma (MM) is a malignant neoplasm of monoclonal plasma cells that accumulate in bone marrow (BM). Malignant pleural effusions (MPE), as part of multiple myeloma clinical presentation, are unusual. Is even more rare as the first sign of presentation, occurring in less than 1% of the cases. The most common associated immunoglobulin with malignant pleural effusions is IgA subtype (80%). This condition carry a poor prognosis. We aim to describe a refractory case of multiple myeloma with extensive disease that presented with extramedullary relapse with malignant pleural effusions , besides discussing the importance of differential diagnosis.

Keywords: Multiple myeloma; Pleural effusion; Differential diagnosis; Humans; Case reports

RESUMO

O mieloma múltiplo (MM) é uma neoplasia maligna de células plasmáticas monoclonais que se acumulam na medula óssea (MO). Os derrames pleurais malignos (EPM), como parte da apresentação clínica do mieloma múltiplo, são incomuns. É ainda mais raro como primeiro sinal de apresentação, ocorrendo em menos de 1% dos casos. A imunoglobulina associada mais comum a derrames pleurais malignos é o subtipo IgA (80%). Esta condição carrega um mau prognóstico. Nosso objetivo é descrever um caso refratário de mieloma múltiplo com doença extensa que apresentou recidiva extramedular com derrame pleural maligno, além de discutir a importância do diagnóstico diferencial.

Descritores: Mieloma múltiplo; Derrame pleural; Diagnóstico diferencial; Humanos; Relato de casos

INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm of monoclonal plasma cells that accumulate in bone marrow (BM), characterized by the SLiM CRAB criteria (≥60% clonal BM plasma cells; serum free Light chain ratio involved:uninvolved ≥100; ≥ 1 focal lesion with ≥5 mm each detected by MRI studies; calcium elevation; renal insufficiency; anemia and bone disease) according with the International Myeloma Working Group (IMWG).

Malignant pleural effusions (MPE), as part of MM clinical presentation, are unusual, observed in about 6% of cases. Is even more rare as the first sign of presentation, occurring in less than 1% of the cases. The most common immunoglobulin associated with MPE is IgA subtype (80%), whereas the remaining cases are mostly IgG type [1,2]. The emphasis regarding pleural effusions in patients with MM rely on the differential diagnosis challenge, besides the poor prognosis when a malignant etiology is defined.

On this setting, we aim to describe the clinical, imaging and pathological presentation of a patient with MPE related to MM, and how the case was conducted.

CASE REPORT

A 62-year-old woman with IgG-lambda type MM came to the emergency room (ER) complaining of progressive dyspnea and dry cough over the previous three days. She was diagnosed with MM one year before, presenting with normocytic anemia (Hemoglobin of 6,7g/dL), renal insufficiency, lytic bone lesions in the left hip, ribs bilaterally and skull, immunoparesis, an 8,1g/dL monoclonal

[1] Hematology Division. Hospital de Clínicas de Porto Alegre, Porto Alegre (RS), Brazil
[2] Hematopathology Division. Hospital de Clínicas de Porto Alegre, Porto Alegre (RS), Brazil
Corresponding author: Júlia Plentz Portich. Hematology Division – Hospital de Clínicas de Porto-Alegre – Ramiro Barcelos, 2350 Porto-Alegre, Rio Grande do Sul, 90035-007, Brazil – (55) 51 3359-8000 – E-,mail: juliaportich@hotmail.com
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peak, and 63% clonal BM plasma cells. The International Staging System (ISS) was III. She was treated with three cycles of cyclophosphamide, thalidomide and dexamethasone (CTD), which was therefore switched to bortezomib, thalidomide and dexamethasone (VTD), until finished five cycles (eight cycles in total), both protocols included bisphosphonates administration. She had a partial response according to IMWG criteria. She also had arterial systemic hypertension with regular treatment, motors sequelae from two previous ischemic strokes, and was an active smoker.

On arrival to ER, pulmonary x-ray and computerized tomography were performed and showed a massive pleural effusion on the right side (Figure 1).

Thoracocentesis removed 1300mL of serosanguinolent fluid, which was sent for analysis. Antibiotic therapy was initiated on suspicion of a parapneumonic origin. After this procedure, the patient had great symptomatic relief. The characteristics presented by the pleural liquid were compatible with exudate by Light's criteria, germs were not isolated and infectious origin has become less likely.

The pleural effusion (PE) smear (Figure 2-A,B) showed numerous mature plasma cells (PC) with eccentric placed nuclei, clumped 'clockface' chromatin, inconspicuous nucleoli and perinuclear hof.

Cell block of PE with hematoxylin and eosin (HE) staining and immunohistochemistry showed numerous plasma cells in bloody background (Figure 2-C) and were positive for CD138, CD38, CD20 (not shown) and lambda light chain (Figure 2-D,E and F), indicating that they were clonal plasma cells. The diagnosis of plasma cell myeloma was made.

She had a premature recurrence of the pleural effusion on the same side, underwenting a pleuroscopy with decortication and pleural drainage by the thoracic surgery team. Pleural biopsy was also performed and confirmed the malignant diagnosis. Besides, flow cytometry of pleural fluid evidenced 80% of clonal plasma cells with the phenotype CD138+, CD38+, CD19-, CD28+, CD27-, CD117-, CD81-, CD56-, CD45+low and cIgLambda+.

During her hospitalization, she also started with a prolonged PT (prothrombin time) and activated partial thromboplastin time (aPTT) without a history of bleeding, with no response to vitamin K administration. Ensuing analysis revealed thrombocytopenia of 43.000 (normal reference value 150.000 to 400.000), low factor V of 41% (70 to 120%) and factor X of 23% (70 to 120%),

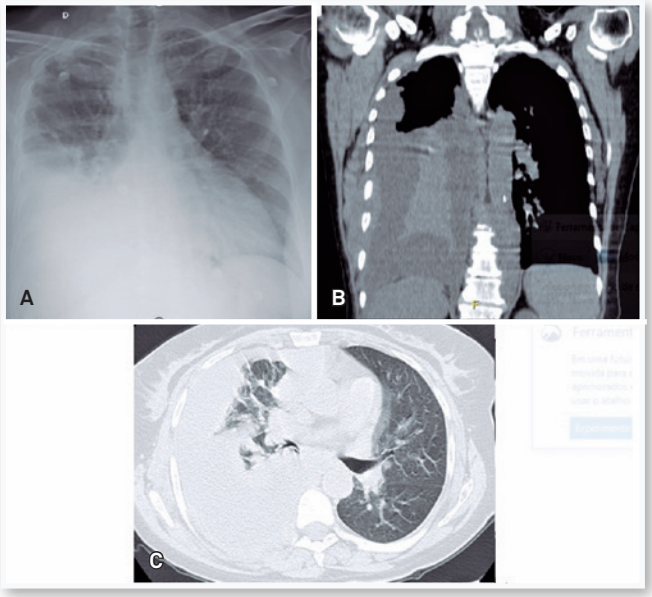

Figure 1. Massive pleural effusion (PE) on the right side, on X-Ray (A); the same PE seem in a coronal label (B) and transversal label (C) of computerized tomography.

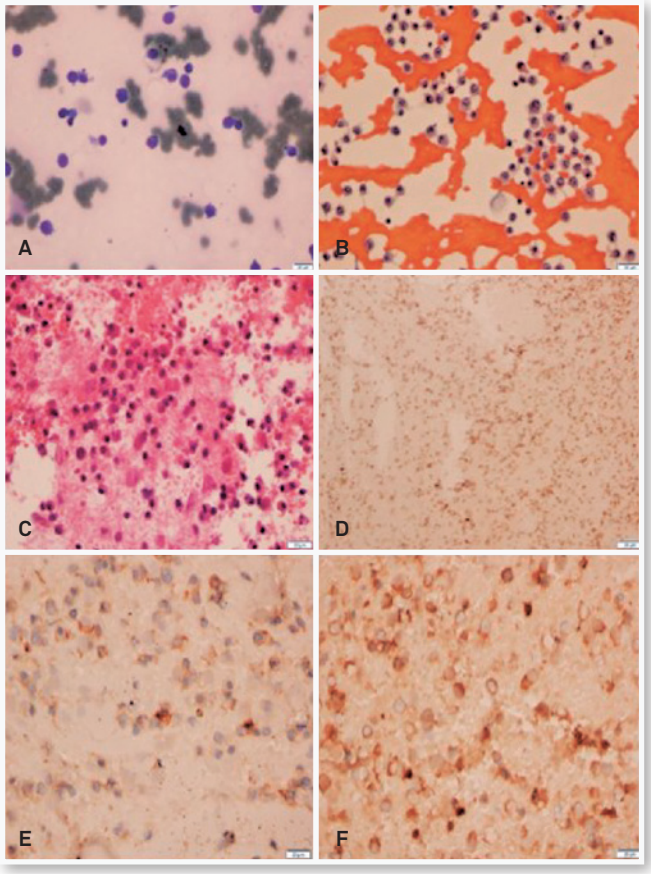

Figure 2. Pleural effusion (PE) smear shows a population of mature plasma cells (PC) with eccentrically placed nuclei, hof perinuclear an inconspicuous nucleoli (MGG 400x) (A) and (Pap 400x) (B); Cell block of PE shows numerous PC in a bloody background (HE 400x) (C); Cell block of PE with immunohistochemistry shows: PC CD138+ (100x) (D); PC CD38+ (400x) (E) and Lambda + (400x) (F).

in addition to low plasma fibrinogen of 102 (200 to 400 mg/dL) and elevated plasma D-dimer 11,26 ug/mL (until 0,5 ug/dL). Based on these findings and the active neoplasm, a diagnosis of disseminated intravascular coagulation (DIC) was made, in addition to deficiency of factor V and factor X associated to MM.

The patient evolved with progressive leukocytosis from 13,150 until 29,260 (3,600 to 11,000) with a predominance of plasmacytes from 2% until 59%, then progressing to a plasmacyte cell leukemia. She had fast and progressive clinical deterioration despite therapeutic strategies. A palliative approach was adopted after discussion with patient and family, and she died after 16 days of inpatient care.

DISCUSSION

Pleural effusion is not uncommon in patients with MM, but is mainly secondary to other causes rather than malignancy itself. In patients with MM, the MPE is a form of extramedullary disease with infiltration of the pleural cavity by plasma cells[3]. It is essential to exclude other justifications, such as nephritic syndrome secondary to renal tubular infiltration and glomerular damage, infections, hypoalbuminemia, pulmonary embolism, congestive heart failure (attention to amyloidosis) and secondary neoplasms.

A diagnostic criterion for MPE was suggested in 1994 by Rodriguez et al[4]. Three parameters were defined to its diagnosis: [1] demonstration of a monoclonal protein in pleural fluid electrophoresis; [2] detection of atypical plasma cells in the pleural fluid; and [3] histological confirmation with a pleural biopsy or by autopsy. Cytological identification of malignant plasma cells within the PE has been considered as the best diagnostic method for MPE, especially on those patients who present with pleural effusion as one of the first signs of the disease[2].

The diagnosis of MM in PE is characterized by a high cellularity with a predominant plasma-cell population present in a bloody and necrotic background; these features are proven to be useful diagnostic findings when founded in the appropriate clinical setting. The cytomorphology of malignant PC includes nuclear polymorphism, prominent nucleoli, and asynchronous maturation of the nucleus in relation to the cytoplasm, being helpful aspects in differentiating reactive from malignant infiltrates. These features are better appreciated in Papanicolaou-stained smears[5]. Immunophenotyping can be an additional tool to determine lineage of abnormal cells. Classically, MM cells express CD38, CD138 and kappa or lambda light chains, but do not express CD19 or CD20. In the event that cytology is unrevealing, pleural biopsy has been used to make an effective diagnosis[6].

The diagnosis on the current case was made based on morphological features on pleural fluid cytology and confirmed with immunohistochemistry on cell block. Morphology of PC can be divided into three categories, mainly based on changes of the nucleus, such as diffuse chromatin pattern, prominent nucleolus, irregular contour of the nuclear membrane, and/or nuclear size larger than expected. These criteria correspond to "immaturity" or "aggressiveness" of the PC clone in MM[7]. In about half of the cases with the so-called "mature" PC subtype, N/C (nucleus/cytoplasm) ratio asynchrony is observed, i.e., presence of one nucleolus, finely dispersed chromatin, and/or irregular nuclear contour contrast with a still large and blue (mature) cytoplasm [7]. Mature myeloma is related to favorable outcome, while immature myeloma, particularly plasmablastyc myeloma, is related to dismal prognosis[8].

Differential diagnosis includes tumors with single dispersed large cells with high N/C ratio, like malignant melanoma, squamous cell carcinoma, and poorly differentiated adenocarcinoma[9]. Additional differential considerations are lymphoid neoplasms with plasmablastyc, immunoblastic, or plasmacytoid morphology, such as diffuse large B-cell lymphoma (DLBCL), ALK-positive DLBCL, plasmablastyc lymphoma (PBL), and primary effusion lymphoma (PEL). The differential diagnosis is even more challenging in the post-hematopoietic stem cell transplant setting, where post-transplant lymphomas can develop[4].

The presence of MPE itself is associated with a poor prognosis, possibly because MPE reflects an invasive form of the disease. The mechanism of pleural disease is poorly understood, but there is a hypothesis based on local invasion from previous osteolytic bone lesions. In the presented case, the patient had previous lesions on 8 and 9th right ribs, precisely the side of the pleural effusion. Traditional chemotherapy regimens tend to be less effective in these patients[2], even when Bortezomib associations are used[10]. Nevertheless, most patients with MPE show relapse within one year and have shorter survival, with a report of 23 cases showing a progression free and overall survival of 5.7 and 11.7 months, respectively[2].

We related a refractory case of MM with extensive disease that presented with extramedullary relapse without conditions for having tried a third line treatment due to its loss of performance status. It is remarkable the unusual manifestations presented in the described case, scenarios associated with a poor prognosis. The cell block stained with HE and immunohistochemistry of PE revealed abnormal plasma cells in MPE and helped to improve the diagnosis.

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