Recurrent pleural effusion in myeloma

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Abstract
Plasma cell (PC) disorders make up a spectrum of diseases which include myeloma and amyloidosis. Pleural effusion in myeloma is rare and may result from myelomatous infiltration of the pleura or heart failure in cardiac amyloidosis. Benign causes of pleural effusion include infection, hypoalbuminemia or chronic renal impairment. Myelomatous pleural effusion (MPE) is diagnosed via pleural fluid cytomorphology and flow cytometry for malignant PCs, protein electrophoresis or pleural biopsy. A 74-year-old man with immunoglobulin A myeloma developed recurrent MPE with possible secondary cardiac amyloidosis. Despite achieving partial remission in serum paraprotein, the effusion was refractory to percutaneous drainage and pleurodesis. The treatment is aimed at eradicating myeloma and relieving respiratory symptoms. Early recognition of myeloma progression into extramedullary infiltration and secondary amyloidosis is important. While chemotherapy intensification in older patients can be challenging, multidisciplinary management is essential in alleviating symptoms and in improving the quality of life.

INTRODUCTION
Pleural effusion during the course of treatment for myeloma may be caused by infection, hypoalbuminemia or chronic renal impairment. Rarely, myeloma may progress into extramedullary infiltration of the pleura or secondary amyloidosis which carries poor prognosis. Treatment with chemotherapy, especially in elderly patients, may cause further morbidity, and the overall condition should be managed within a multidisciplinary setting.

CASE REPORT
A previously fit 74-year-old male presented with lethargy and reduced effort tolerance for 1 month. He had normochromic normocytic anemia (8.3 g/dl), raised creatinine (143 μmol/l), hypercalcemia (3.34 mmol/l), hypoalbuminemia (27 g/l) and normal lactate dehydrogenase level. He was diagnosed with R-ISS Stage II multiple myeloma (MM) following the detection of serum monoclonal paraproteinaemia immunoglobulin A (IgA) Kappa (37 g/l) and Bence Jones protein 789 mg/l. Bone marrow (BM) biopsy demonstrated 47% plasma cells (PCs) infiltration with positivity toward CD138 and Kappa light chain restriction. Cytogenetic analysis revealed normal karyotype, however, fluorescence in situ hybridization detected deletion 13q and an extra copy of TP53 gene in 55% of the cells analyzed. The beta-2 microglobulin was raised by 7.2 mg/l. Positron emission tomography-computed tomography (PET-CT) scan demonstrated no bone lesions, however, there was right-sided pleural effusion (Fig. 1) possibly due to inadvertent fluid overload secondary to hyperhydration for hypercalcemia, which resolved with frusemide on subsequent chest X-ray (Fig. 2A). A baseline echocardiogram was normal.

After completion of the first chemotherapy cycle, which consisted of bortezomib, cyclophosphamide and dexamethasone, he developed atrial fibrillation (AF) and dyspnea. Chest X-ray showed mild bilateral pleural effusion (Fig. 2B). Echocardiogram detected concentric left ventricular (LV) hypertrophy with 15-mm thickness and dilated left atrium (Fig. 3A and B). The ejection fraction was preserved at 59%. Tissue doppler imaging of the septal wall showed reduced septal velocity of 4 cm/s and elevated E/e’ value of 19.49, with apical sparing pattern and reduced global longitudinal strain value of ~16.8% (Fig. 4A and B). Myeloma-associated cardiac amyloidosis was suspected. The serum pro B-type natriuretic peptide (pro-BNP) was elevated at >9000 pg/ml, however, a troponin level was not available. BM trephine and transcutaneous fat pad biopsies were negative for Congo red stain. CT scan revealed no hepatomegaly or pulmonary alveolar infiltrate. Cardiac...
PET-CT scan demonstrated right-sided pleural effusion due to inadvertent fluid overload secondary to hyperhydration for hypercalcemia.

Figure 2. (A, B) Chest x-ray with clear bilateral lung fields after treatment with frusemide (A); presence of bilateral mild pleural effusion upon completion of first chemotherapy cycle with concurrent development of AF and dyspnea (B).

Figure 3. (A, B) Transthoracic echocardiographic 2D images. Parasternal long axis view showing concentric LV hypertrophy and dilated left atrium (A). Apical four chamber view showing concentric LV hypertrophy and biatrial enlargement (B).

magnetic resonance imaging (MRI) was requested from another institution as this modality was not available in our center, however, the patient was too unwell to travel.

A diagnostic thoracentesis revealed straw-colored pleural fluid. The cytology showed presence of mesothelial cells, foamy macrophages, lymphocytes, neutrophils and dysplastic PCs (Fig. 5). The effusion was transudative and the cultures were negative for microorganism growth. Pleural fluid immunophenotyping was performed using FACS Lyric flow cytometer system (Becton-Dickinson, Erembodegem, Belgium) which showed gated cells positivity for CD45 (dim), CD19, CD138 (bright) and aberrant expression of CD56, consistent with myelomatous pleural effusion (MPE; Fig. 6).

The patient made a symptomatic recovery and resumed chemotherapy. He achieved partial remission after two cycles of chemotherapy with paraprotein reduction to 6.6 g/l. Unfortunately, the malignant effusion recurred a month later. Bilateral seldinger tubes (12Fr) were inserted with cumulative pleural fluid drainage of 5200 ml on the right and 4250 ml on the left, followed by left talc pleurodesis, and the left chest drain was successfully removed. However, he continued to have persistent drainage on the right, and an indwelling pleural catheter was considered. Lenalidomide was introduced as a part of VRD chemotherapy to salvage the disease. The option of radiotherapy was discussed, however, the patient continued to deteriorate with sepsis and succumbed a few weeks later.

DISCUSSION

Pleural effusion occurred in 6% of MM patients predominantly due to amyloidosis-related congestive heart failure, while other causes include MPE, infection, hypoalbuminemia and chronic renal failure [1]. MPE is a rare extramedullary manifestation associated with poor prognosis. The incidence of MPE was 2.65% with a median survival of 2.47 months and occurred at median age of 50 years with a male predominance [2]. MPE was the presenting feature in 45.45% of patients, predominantly unilateral in 81.8% patients, and the majority of the disease subtype was IgG Kappa [2]. We report a patient with IgA MM who developed MPE with possible secondary cardiac amyloidosis.

The diagnosis of MPE requires demonstration of neoplastic PC on pleural fluid cytology, immunophenotyping, pleural fluid electrophoresis or pleural biopsy [3]. Differentiating neoplastic from reactive PC can be morphologically challenging, especially in the presence of cellular degeneration or inadequate sample size. Immunophenotyping provides diagnostic precision by detecting aberrant antigen expression on malignant PC, especially in patients with negative cytology [4, 5]. Normal PC express CD38 and CD138, while malignant PCs may also express CD19, CD45 or CD56 with light chain restriction [6]. Our patient demonstrated transudative pleural effusion with morphologically dysplastic PC positive for CD19, CD38, CD 138, CD45 and CD56.

Concomitant AF, elevated pro-BNP and LV hypertrophy raised the suspicion of cardiac amyloidosis, which may also have contributed to the patient’s recurrent pleural effusion. Up to 30% of patients with MM have sub-clinical amyloid deposits, while 15% may suffer from overt amyloidosis [7]. Cardiac amyloidosis may be diagnosed non-invasively by cardiac MRI or nuclear scintigraphy [8]. Biopsy of endomyocardial tissue may be needed in equivocal cases or discordant data. Abdominal fat aspirate can be performed, where Congo red stain will detect 70–90%
Figure 4. (A, B) Tissue doppler imaging of the septal wall showing reduced septal velocity of 4 cm/s and elevated E/e' value of 19.49 (A). Bulls-eye figure of LV peak systolic strain values showing apical sparing pattern (cherry on top pattern) with reduced global longitudinal strain value of $-16.8\%$ (normal value 22%) (B).

Figure 5. Pleural fluid cytology with numerous PCs (red arrow) and mesothelial cells (yellow arrowhead; MGG stain 40×).

Figure 6. Flow cytometry plot showing immunophenotyping of pleural fluid. The gated cells were positive for CD38 and CD138 with bright expression (6%). They were negative for CD19. A small population was positive for CD56 (3%; not shown in plot).

of which may be demonstrated with pleural tissue biopsy via closed percutaneous route or thoracoscopy [9].

MPE predicts poor outcomes with a short survival time [2]. Treatment is directed at eliminating myeloma with systemic chemotherapy, while symptomatic therapy, such as diuretics, thoracentesis and pleurodesis, may provide some relief to improve the quality of life. Despite reduction in serum paraprotein with bortezomib-based chemotherapy, the patient required multiple admissions for thoracentesis and pleurodesis for the refractory effusion. In the era of novel agents, patients with extramedullary involvement respond poorly to therapy, indicating the biological differences between intramedullary and extramedullary disease. Although pleurodesis has a reported success rate of 87–90% in both malignant and non-malignant effusion [10], myeloma infiltration in the pleural cavity carry a short median survival of 1.5–3 months [3].

Aggressive chemotherapy, including stem cell transplantation, should be considered, especially in younger and fit patients. Unfortunately, this approach is not readily applicable in the elderly with co-morbidities and poor performance status. Multidisciplinary approach and palliative therapy with pleural drainage or pleurodesis provide symptomatic relief and reduce the pleural fluid accumulation.

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CONFLICT OF INTEREST STATEMENT

None declared.

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