case report

Pleural myelomatous involvement in multiple myeloma: five cases

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Pleural myelomatous involvement in multiple myeloma (MM) is rare, occurring in less than 1% of cases. We retrospectively studied five cases of patients with MM who developed myelomatous pleural effusions. Three men and 2 women with a mean age of 61 years presented with myelomatous pleural effusion. The pleural fluid electrophoresis revealed a peak of IgG in three cases, of IgA in one case, and of lambda light chains in one case, which were identical to that in the sera of the patients. Detection of typical plasma cells in pleural fluid cytology was contributive, and histologic confirmation by pleural biopsy was positive in four cases. Treatment consisted of chemotherapy. The clinical outcome was initially good, but relapses occurred in all cases early and were complicated by fatal infections. Myelomatous pleural effusion is a rare affection. It is usually a late complication associated with poor prognosis.

Multiple myeloma (MM) is a malignant proliferation of plasma cells that usually invades the bone marrow, but involves other areas as well. One kind of thoracic involvement is pleural effusion. In 6% of patients with myeloma, pleural effusions developed (myelomatous and non myelomatous).[1] Myelomatous pleural effusions are rare, with approximately 80 cases reported worldwide.[2,3] We present 5 cases of patients with MM who developed myelomatous pleural effusions (**Table 1**). We analyzed the clinical presentation and outcome of this association.

CASE 1

A 74-year-old male patient without medical history was admitted to our department in June 2007 for diffuse bone pain. Low back pain had started a few months before and progressed to severe disability. He had lost more than 10 kg of body weight over the previous three months. Physical examination was normal. Laboratory studies revealed a normal cell blood count and blood chemistry values, including serum calcium, were within normal ranges. Serum electrophoresis revealed a gamma M component, and serum immune electrophoresis demonstrated IgA monoclonal protein. Radiographic examination showed osteolytic punched-out lesions in the skull and pelvis. Bone marrow aspiration revealed 57% of dystrophic plasmocytosis. The diagnosis of multiple myeloma stage III was accepted. Melphalan-prednisone chemotherapy was started. Two months after the administration of the final course of chemotherapy, the patient was readmitted for chest pain and dry cough without fever or sputum production. Chest X-ray showed pleural effusion. Chest CT scan revealed a scalloped aspect of the pleura with bilateral effusion, thus leading to the conclusion of myelomatous pleural effusion. Unfortunately, neither thoracocentesis nor pleural biopsy were made. The patient left the hospital against medical advice and was lost to follow-up.

CASE 2

A 62-year-old male patient, with a medical history of non-insulin-dependent diabetes, was hospitalized in 2001 for bone pain with unencrypted emaciation. He reported a three-month history of dull right lower chest pain which was not made worse by coughing or deep inspiration. No hemoptysis or fever was present. Physical examination revealed dullness and decreased breath sound at the base of the right lung. Laboratory data showed an erythrocyte sedimentation rate of 30 at the first hour, a normal range of serum calcium, hy-

pogammaglobulinemia on serum electrophoresis, and monoclonal lambda light chains on serum immune electrophoresis. There was no Bence-Jones proteinuria. Radiographic examination showed osteolytic punched-out lesions in the skull and in the second lumbar vertebra, and mild pleural effusion at the base of the right lung. Lumbar CT scan revealed multiple osteolytic lesions on the first, second and third lumbar vertebrae. Bone marrow aspiration revealed 62% dystrophic plasma cell infiltration. The diagnosis of multiple myeloma stage II-a was accepted. Thoracocentesis yielded exudative effusion. Cytology revealed an increase in atypical plasma cells (**Figure 1**). Immune fixation of proteins in pleural fluid showed monoclonal lambda light chains. Pleural biopsy confirmed the plasmocyte infiltration. The patient was diagnosed with light chain kappa type MM and underwent poly-chemotherapy with vincristine, adriamycin and dexamethasone. Two weeks later, chest X-ray showed an improvement in the pleural effusion. A few months later, the effusion increased again and the disease worsened. The patient died of serious infectious complications.

CASE 3

A 62-year-old woman complained of diffuse bone pain and fatigue of several months. Her complaints had increased slowly. Nothing significant was observed in her personal or family medical history. Examination of her respiratory system, cardiovascular system, central nervous system, and GI system revealed no abnormal findings. There was no lymphadenopathy. Laboratory findings showed an elevated erythrocyte sedimentation rate, gamma M component on serum electrophoresis, monoclonal IgG kappa light chain on serum immune electrophoresis, and a normal range of serum calcium. Conventional radiographs showed osteolytic punched-out lesions in the skull and pelvis. Bone marrow aspiration revealed 60% dystrophic plasmocytosis. The diagnosis of multiple myeloma stage III-a was accepted. A six-month polychemotherapy (melphalan, cyclophosphamide and dexamethasone) was carried out with an initial clinical improvement. Five months later, the patient presented with shortness of breath and chest pain. Examination of the respiratory system revealed decreased breath sounds in the lower right hemithorax, with dullness to percussion. The rest of the physical examination was normal. Chest X-ray showed a right pleural effusion. Thoracocentesis yielded exudative effusion with multiple atypical plasmocytes. Immune fixation of proteins in pleural fluid showed monoclonal IgG kappa light chain. Pleural biopsy confirmed the plasmocyte infiltration. The patient was admitted to the intensive unit care and died a few days later of acute respiratory distress.

CASE 4

A 52-year-old man presented to the emergency department with exertional dyspnea, pleuritic chest pain

Table 1. Characteristics of our patients with pleural involvement by multiple myeloma.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Gender	74/Male	62/Male	62/Female	52/Male	55/Male
Inaugural symptoms	Back pain	Emaciation Chest pain	Bone pain Fatigue	Dyspnea	Back pain Dyspnea
Monoclonal gamma globulin type	Ig A	lambda light chain	Ig G kappa	Ig G kappa	Ig G lambda
Multiple myeloma stage	IIIa	IIa	IIIa	IIa	IIa
Myelomatous pleural effusion delay	2 months	Inaugural	5 months	Inaugural	Inaugural
Thoracocentesis findings	Not performed	Exudative effusion Monoclonal Lambda light chain in pleural fluid Plasmocyte infiltration on pleural biopsy	Exudative effusion and plasmocytes in pleural fluid Monoclonal Ig G in pleural fluid Plasmocyte infiltration on pleural biopsy	Exudative effusion plasmocytes in pleural fluid Monoclonal Ig G in pleural fluid Plasmocyte infiltration	Exudative effusion plasmocytes in pleural fluid Monoclonal Ig G in pleural fluid Plasmocyte infiltration
Treatment	Melphalan Prednisone	Vincristine Adriamycin Dexamethasone	Melphalan Cyclophosphamide Dexamethasone	Vincristine Adriamycin Dexamethasone	Melphalan Prednisone
Outcome	Lost of sight	Dead	Dead	Dead	Dead

and dry cough. He had been on a trial antibiotic treatment, which did not alleviate his complaints. Physical examination was normal apart from decreased breath sounds and percussion dullness over the right lung. The only abnormality in blood cell count analysis was mild leukocytosis. Blood chemistry including calcium level was within normal range except a gamma M component on serum electrophoresis and IgG kappa light chain on immune serum electrophoresis. Standard radiographs showed osteolytic punched-out lesions in the skull, and a right basal pleural effusion. Bone marrow aspiration revealed 52% dystrophic plasmocytosis. Thoracocentesis yielded exudative effusion with multiple atypical plasmocytes. Immune fixation of proteins in pleural fluid showed monoclonal IgG kappa light chain. Pleural biopsy confirmed the plasmocyte infiltration. The patient received three cures of polychemotherapy with vincristine, adriamycin, and dexamethasone, but no response was observed and his disease worsened. He died 4 months later of acute respiratory distress.

CASE 5

A 55-year-old male patient presented to our department complaining of shortness of breath and low back pain. On physical examination, blood pressure was 100/60, heart rate 96/min, respiratory rate 24/min, and temperature 39°C. Examination of the respiratory system revealed decreased breath sounds and percussion dullness over the left lung. Blood chemistry including calcium level was within normal range except a gamma M component on serum electrophoresis and IgG lambda light chain on serum immune electrophoresis. Standard radiographs showed osteolytic punched-out lesions in the skull, and a left basal pleural effusion. Bone marrow aspiration revealed a dystrophic plasmocytosis. Thoracocentesis yielded exudative effusion with atypical plasmocytes. Immune fixation of proteins in pleural fluid showed monoclonal IgG lambda light chains. Pleural biopsy confirmed the plasmocyte infiltration. Melphalan-prednisone chemotherapy was started. The patient improved initially but died a few months later of septicemia.

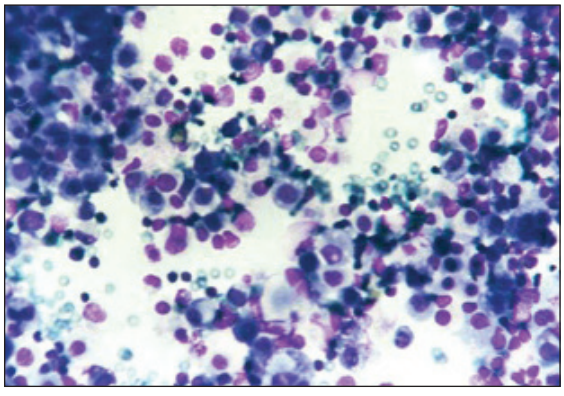

Figure 1. Cytology of pleural effusion showing the presence of atypical plasma cells.

DISCUSSION

Pleural effusion occurs in 6% patients with MM.[1] The etiology is multifactorial, and effusions due to pleural myelomatous involvement are rare, occurring in less than 1% of the cases.[2] Common causes of pleural effusions in MM include congestive heart failure due to hyperviscosity or amyloidosis, renal failure, pulmonary embolism due to a hypercoagulable state or plasma embolization, a secondary neoplasm such as mesothelioma, infections due to immunosuppresion (pneumonia, tuberculosis, AIDS, other viral illnesses), and chylothorax or bleeding.[4-7] Several criteria must be fulfilled to assert the myelomatous origin of the pleural effusion. The presence of plasma cells in pleural fluid is a fundamental criterion and the use of Wright stain enhances the identification of these cells.[8] The detection in pleural fluid of monoclonal immunoglobulin identical to that of serum is not an essential criterion; it does not allow its malignant nature to be asserted because it can be produced locally. Pleural biopsy may reveal a plasma cell infiltration[9] but it is not necessary for diagnosis 2 as, due to discontinuous myeloma lesions, it can be noncontributory.[2] To our knowledge, respectively 32 cases and 47 cases of myelomatous pleural effusion have been reported in the English[10] and Japanese literature.[11] Our experience with 235 myeloma patients involved 5 cases (3.6%), inaugural in three cases, IgG type MM in three cases, IgA type in one case, and lambda light chain type in one case. In the literature reporting myelomatous pleural effusions, 80% of them were due to IgA, perhaps as a result of its major tendency to invade extraosseous structures.[2] However, Meoli et al, in a review of the literature, reported a predominance of IgG myeloma.[12] Pleural effusions due to plasma cell infiltration are rare and may result from extension of adjacent subcutaneous plasmocytomas, skeletal plasmocytomas, adjacent parenchymal plasmocytomas into the pleural space, or direct implantation into the pleura.[13] Therefore, it was suggested that the major determining factor in the development of myelomatous effusion is the production of large quantities of immunoglobulin by malignant plasma cells in or near the pleura, which raise the colloid osmotic pressure of the fluid to such a level that normal absorption cannot take place.[14] Kazuhiko et al were interested in chromosomal abnormalities in a case of MM with myelomatous pleural involvement

and concluded with a variety of chromosomal abnormalities; a translocation involving the immunoglobulin heavy chain (Ig H) region at chromosome region 14q32 which is regularly involved in human B cell malignancies and may upregulate existing oncogenes or create new hybrid genes with transforming properties.[15] 14q32 was detected in 74% of patients with MM, by fluorescence in situ hybridization and it is one of the factors related to poor prognosis.[16] These translocations are found in the earliest stage of the disease, suggesting that they are an early and possibly initiating event in the disease development. The detection of genetic changes is important, not only because of their associations with clinical prognosis, but also because they can be used as measurable targets for response to treatment.[16] Treatment of myelomatous pleural effusion is not codified and uses systemic chemotherapy, sometimes associated with radiotherapy in case of local invasion,[9] or local treatment by intrapleural injection of methylprednisolone, adriamycin and interferon.[8] The pleural talc pleurodesis may be necessary in some cases of recurrent pleural effusions. Myelomatous pleural effusion is characterized by its recurrence and inexhaustible nature. Its occurrence is a factor of poor prognosis and median survival does not appear to exceed four months from the date of discovery, all treatments being combined.[12,17] However, favorable outcomes have been reported, with a survival exceeding nine months.[9,18,19]

CONCLUSION

Malignant effusions in myeloma patients are associated with poor prognosis. Affected patients are usually resistant to treatment and often relapse in spite of aggressive chemotherapy necessitating pleurodesis. despite the wide choice of available therapeutic measures our patients died.

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