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CASE REPORT

Malignant myelomatous pleural effusion-Is onset of effusion a new prognostic factor?

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ABSTRACT

Malignant pleural effusion in myeloma (MMPE) is a rare terminal event; with a median survival is four months. All the patients usually have multiple poor prognostic factors and none of them (like beta 2-microglobulin, karyotype, Stage of disease, C-reactive protein etc.) correctly predicts the survival. We are reporting a series of five cases and evaluated the factors influencing the overall survival. All of our patients had a very good response to treatment and had a better survival compared to the reported cases so far. After reviewing the literature carefully we found that timing of development of pleural effusion is probably the most important prognostic factor. Those who develop effusion after some time lag form the initial treatment, will have a poor survival (median four months) compared to those who had effusion at the start of the disease.

Key Words: Myeloma, pleural effusion, survival

INTRODUCTION

Pleural effusion is an occasional complication in patients with multiple myeloma. It has a varied etiology ranging from benign causes like congestive heart failure, infections, etc. to malignant pleural effusion, the latter being extremely rare, with only 91 cases reported as of the end of August 2005[1]. Medline search added four more cases following this report[2-5], making the total reported cases 95 thus far. Development of effusion in myeloma patients carries a poor prognosis irrespective of the etiology. The term "malignant myelomatous pleural effusion (MMPE)" is used restrictively in that subset of patients in whom malignant myeloma cells are identified in cytological examination of the pleural fluid or by pleural biopsy[1]. Whenever a patient develops MMPE, the median survival is usually less than four months in the majority of the cases[6]. We report a single institute's experience with this rare event, the clinico-hematological characteristics, response to therapy and survival data.

This is a retrospective analysis of the case records. The study was conducted at Kidwai Memorial Institute of Oncology, Bangalore, India, a tertiary care cancer center with annual attendance of 16.000 new cases. A total of five patients had MMPE in the past eight years (1997-2005). The clinical characteristics, treatment received, and the response were evaluated. Myeloma was diagnosed if the patient fulfilled at least two major criteria or one major and two minor criteria as defined[7]. Durie and Salmon staging system was used to stage the disease[8]. Diagnosis of myelomatous pleural effusion was based on the demonstration of malignant plasma cells in the pleural fluid. Though other means like demonstration of raised immunoglobulin levels higher than that found in plasma are used, we did not adopt those criteria. At baseline, we performed a plain chest X-ray, skeletal survey, serum immunoglobulin measurement, bone marrow examination and serum chemistry. Though beta-2-microglobulin is an established prognostic marker, results were available in only three patients. All the tests done at baseline were repeated at follow-up. Bone marrow cytogenetics (conventional) was done in all patients. However, in view of non-availability, we did not perform fluorescent in situ hybridization (FISH). C-reactive protein (CRP) was not a routine practice at our institute and thus was not done. We followed a standard protocol comprising cyclophosphamide (650 mg/m^2), vincristine (1.4 mg/m^2), and prednisone (60 mg/m^2) every three weeks for six cycles (COP). Though we offered induction with vincristine, adriamycin and dexamethasone (VAD) followed by high-dose chemotherapy with melphalan and stem cell support, none of our patients could afford it. Therefore, no patient was shifted from the COP treatment. A Southwest Oncology Group (SWOG) criterion was used to assess the response to therapy.

Case 1

A 64-year-old male presented with complaints of generalized body pains and rapidly increasing breathlessness for eight months. Examination findings included massive pleural effusion, with systemic examination findings normal. Chest X-ray showed right-sided massive effusion. Pleural fluid aspiration cytology suggested malignant plasma cells. The laboratory parameters of the patient were: hemoglobin 8.2 g/dL, creatinine 2.9 mg/dL, and calcium 12.8 mg/dL, with other biochemical parameters normal. Skeletal survey showed multiple lytic lesions involving D8, 9, L1, 2 vertebrae, 7^{th} and 8^{th} ribs on right side, both iliac bones and skull. Serum electrophoresis showed Ig G of 7.4 g/dL. Urine Bence-Jones protein test was positive. The serum albumin was 2.8 g/dL. Bone marrow showed 38% immature plasma cells. Cytogenetics from marrow revealed normal karyotype. The beta-2-microglobulin was 3.9 ng/cmm. He was diagnosed as having MMPE with stage III B or III by International Staging System [ISS]. The patient was started on COP and his pleural effusion res-

ponded after two courses. By the end of six cycles, there was no evidence of effusion and IgG levels reduced to 2.0 g/dL and bone marrow was in complete remission. The beta-2-microglobulin was reduced to 1.9 ng/cmm. He remained asymptomatic for the next seven months, after which he was lost to follow-up.

Case 2

A 63-year-old female presented with intermittent backache and dyspnea for seven months. She did not have any pallor, jaundice, lymphadenopathy or organomegaly. Examination of chest suggested massive pleural effusion. Her hemoglobin was 6.8 g-%, serum calcium 13.6, and creatinine was 3.1 mg/dL. The protein electrophoresis showed IgG monoclonal band with levels of 8.6 g/dL. Computerized tomography (CT) scan of the thorax showed massive pleural effusion. Pleural fluid cytology showed malignant plasma cells. Skeletal survey showed a collapse of D6, 7, 8 vertebrae and multiple lytic lesions in the lateral view of the skull X-ray. Bone marrow aspiration was done and showed 25% immature plasma cells. Urine Bence-Jones protein test was positive. The serum albumin was 2.6 g/dL. Cytogenetics revealed 46 XX-13q[8] and the beta-2-microglobulin was 5.5 ng/cmm. She was diagnosed as having MMPE with stage III B (Durie-Salmon staging) or III by ISS. The patient was started on COP for six cycles. Her pleural effusion responded after four cycles and there was no evidence of effusion after four cycles. The IgG levels reduced to 2.2 g/dL, and bone marrow showed 5% mature plasma cells; however, beta-2-microglobulin was still high at 2.5 ng/cmm. She remained asymptomatic for the next 11 months, after which she was lost to follow-up.

Case 3

A 66-year-old male farmer presented with a seven-month history of pleuritic chest pain and breathlessness. He had history of smoking and significant weight loss over the last couple of months. Examination showed massive pleural effusion, and the evaluation done at another facility showed right-sided pleural effusion on chest X-ray and multiple lytic lesions on skeletal survey. Pleural fluid aspiration suggested malignant plasma cells. He was then referred to our hospital for further management. On admission, hemoglobin was 7.2 g/dL, white blood count 8100/cumm with normal differential count and platelets 255.000/cumm, creatinine 2.5 mg/dL, and calcium 13.1 mg/dL, with other biochemical parameters normal. His total protein was 9.8 g/dL and serum protein electrophoresis showed monoclonal spike in gamma region. Serum immunofixation electrophoresis showed IgG of 7.0 g/dL. Urine Bence-Jones protein test was positive. The serum albumin was 2.6 g/dL. Bone marrow showed plasma cells of 30%. Cytogenetics revealed normal karyotype and the beta-2-microglobulin was 4.5 ng/cmm. He was diagnosed as having MMPE with stage III B Durie-Salmon staging or III by ISS. The patient was started on COP. His pleural effusion responded after four cycles with a major response (> 75% reduction); however, X-ray still showed evidence of effusion. The IgG levels reduced to 1.8 g/dL with bone marrow showing 10% plasma cells. He remained asymptomatic for the next seven months. Six months later the patient presented with high-grade fever and was diagnosed as having gram-negative septicemia. He died within 36 hours of the hospital admission before any evaluation of the disease status could be carried out.

Case 4

A 69-year-old male laborer presented with a six-month history of breathlessness and generalized body pains. He also complained of dry cough for the same duration for which he was taking antituberculous therapy as prescribed by the local doctor. However, as there was no improvement he consulted the outpatient department of our institute. Examination of the patient showed massive pleural effusion. Chest X-ray showed left-sided massive effusion and the pleural fluid aspiration cyto-

logy suggested malignant plasma cells. His hemoglobin was 8.9 g/dL, creatinine 2.4 mg/dL, and calcium 13.9 mg/dL, with other biochemical parameters normal. Urine Bence-Jones protein test was positive. The serum albumin was 2.5 g/dL. Skeletal survey showed multiple lytic lesions involving D5, 6, L1, 2 vertebrae, bilateral ribs, skull and both iliac bones. Serum electrophoresis showed IgG of 8.4 g/dL. Bone marrow showed 45% immature plasma cells. Cytogenetics from marrow revealed 46 XY, -3q, -13q[6]. The beta-2-microglobulin was 4.8 ng/cmm. He was diagnosed as having MMPE with stage III B (Durie-Salmon staging) or III by ISS. The patient was started on COP. After six months of therapy, the Ig G levels reduced to 1.8 g/d, bone marrow showed only 8% mature plasma cells, serum beta-2-microglobulin was 2.8 ng/cmm and X-ray showed no evidence of effusion. He remained asymptomatic for the next five months. During the follow-up he was found to have recurrent effusion and increasing levels of IgG and was therefore offered the next line of therapy. However, the patient refused further treatment and died in the next one-month period due to progressive disease.

Case 5

A 67-year-old male teacher presented with a five-month history of generalized body pains. He had anorexia and weight loss for roughly the same duration. Positive findings in the patient were minimal right-sided pleural effusion and clubbing. CT scans showed right-sided minimal effusion and CT-guided aspiration cytology suggested malignant plasma cells. His hemoglobin was 6.9 g/dL, creatinine 2.8 mg/dL, and calcium 12.9 mg/dL, with other biochemical parameters normal. Skeletal survey showed multiple lytic lesions involving skull and both iliac bones. Serum electrophoresis showed IgG of 7.4 g/dL. Urine Bence-Jones protein test was positive. The serum albumin was 2.2 g/dL. Bone marrow showed 55% immature plasma cells. Cytogenetics from marrow revealed normal karyotype. The beta-2-microglobulin was 3.8 ng/cmm. The patient was started on COP. His pleural effusion showed partial response and IgG levels reduced to 1.2 g/dL; bone marrow showed 18% plasma cells. He remained asymptomatic for the next five months. During the follow–up, he was found to have plasmacytoma of the skull bone compressing the brain parenchyma. Local radiotherapy was started for the patient as he refused surgery. However, the patient died in one week with features of increased intracranial tension due to progressive disease.

DISCUSSION

The reported incidence of pleural effusion in myeloma patients is 0.8% of all newly diagnosed cases[9]. However, taking the number of new myeloma cases diagnosed per year (approximately 40.000 per year-US data) into consideration, the total reported cases of MMPE is far less[1-6]. The reasons for this huge disparity could be

1. Under-reporting of this terminal event or
2. Over-estimation in the Mayo clinic data (which appears more likely), which might not truly represent the general population.

The presenting symptom in the majority of the cases was dyspnea in our series, similar to the current literature (median duration of symptoms around seven months)[1-6]. Though the exact etiology of this rare event is not clear, multiple hypotheses exist, such as invasion from adjacent skeletal lesions or direct pleural involvement by myeloma[1]. We based our diagnosis on cytology of the pleural fluid, rather than measuring the immunoglobulin levels or doing a biopsy, as the former is equally sensitive[10]. Therefore, in the present series, we did not have data on the immunoglobulin levels in the pleural fluid. The greatest challenge of this entity is to determine the reasons for such poor outcome and to define the prognostic factors in this disease. For the same reason, we thoroughly searched the literature for the management protocols followed in each case and

the prognostic factors wherever stated. There is no uniformity in the protocols followed to treat this condition. The commonest modalities tried are:

1. Intra-pleural chemotherapy[11]
2. Radiation therapy to the chest[12]
3. Systemic therapy[1]

The results of response rates and survival were similar with all these modalities. However, in the present series, we observed a significantly better outcome compared to the historical controls (the median survival was four months after diagnosis). Therefore, we attempted to investigate the prognostic factors and patient characteristics of the present series and to compare with the cases reported to date. Complete data was not available in most of the series, with only a few authors stratifying the patients based on the known risk factors (i.e. beta-2-microglobulins, plasma cell labeling index, serum albumin, calcium, creatinine level, hemoglobin, presence of cytogenetic abnormalities, etc.)[1-5]. The most consistent finding in almost all cases was advanced disease and multiple poor prognostic factors. In the present series also, all the patients had stage III disease and harbored multiple poor prognostic markers. However, contrary to the expected 15-month survival in stage III myeloma, patients with effusion will have a shorter survival of around four months. Therefore, it is not very clear how far these factors play a role in determining the outcome. A careful review of the available 91 cases suggested that the survival can be as high as 50 months in a subset of patients who had effusion at the time of presentation (initial diagnosis of myeloma). The majority of the patients who developed effusion in the course of therapy or just after therapy had poor prognosis, with median survival of around four months. As all our patients had effusion at the time of diagnosis, all of them had higher survival (median 10 months) than that reported in the literature, as would be expected. Therefore, timing of development of malignant effusion is probably an important prognostic marker.

In conclusion, timing of development of pleural effusion is probably the most important prognostic factor. Those who develop effusion after some time lag from the initial treatment will have a poor survival (median 4 months) compared to those who had effusion at the start of the disease.

REFERENCES

1. Kamble R, Wilson CS, Fassas A. Malignant pleural effusion of myeloma: Prognostic factors and outcome. Leuk Lymph 2005;46:1137-42.
2. Ghosh S, Gopal R, Advani SH. Myelomatous pleural effusion. J Assoc Physicians India 2006;54:738-9.
3. Crespo Valades E, Espinosa de los Monteros Garde MJ. Myelomatous plural effusion. An Med Interna 2005;22:550-1.
4. Ulubay G, Eyuboglu FO, Simsek A, Ozyilkan O. Multiple myeloma with pleural involvement: A case report. Am J Clin Oncol 2005;28:429-30.
5. Gogia A, Agarwal PK, Jain S, Jain KP. Myelomatous pleural effusion. J Assoc Physicians India 2005;53:734-6.
6. Kim YM, Lee KK, Oh HS, Park SK, Won JH, Hong DS, Park HS, Park JS, Lee DW. Myelomatous pleural effusion with poor response to chemotherapy. J Korean Med Sci 2000;15:243-6.
7. Kyle R. Diagnostic criteria of multiple myeloma. Hematol Oncol Clin North Am 1992;6:347-58.
8. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Cancer 1975;36:842-54.
9. Kintzer JS, Rosenow EC, Kyle RA. Thoracic and pulmonary abnormalities in multiple myeloma. Arch Intern Med 1978;138:727-30.
10. Sasser RL, Yam LT, Li C. Myeloma with involvement of the serous cavities. Acta Cytol 1990;34:479-85.
11. Makino S, Yamahara S, Nagake Y, et al. Bence-Jones myeloma with pleural effusion: Response to alpha-interferon and combined chemotherapy. Int Med 1992;31:617-21.
12. Favis EA, Kerman HD, Schildecker W. Multiple myeloma manifested as a problem in the diagnosis of pulmonary disease. Am J Med 1960;28:323-32.