**Bence-Jones Myeloma with Pleural Effusion: Response to α-Interferon and Combined Chemotherapy**

Shinya Makino, Shigehiro Yamahara, Yoshio Nagake and Junta Kamura

A 73-year-old female patient with myelomatous pleural effusions is described. She was admitted to our hospital with lumbago and emaciation. Laboratory findings revealed cytopenia and hypogammaglobulinemia. Immunoelectrophoresis demonstrated Bence-Jones monoclonal protein in the serum, but not in the urine. Bence-Jones myeloma was diagnosed by the bone marrow aspiration. Chest X-ray film, however, showed bilateral pleural effusions. Fluid cytology revealed numerous immature plasma cells, indicating pleural involvement. Intrapleural administration of α-interferon combined with systemic chemotherapy (oral melphalan-prednisolone with α-interferon im.) was successful in maintaining the resolution of pleural effusions. Intrapleural α-interferon administration seems to be effective in the management of myelomatous pleural effusions.

*Internal Medicine* 31: 617–621, 1992

**Key words:** multiple myeloma, intrapleural administration

**Introduction**

Pleural effusion due to malignant plasma cell proliferation is an uncommon manifestation of multiple myeloma (1, 2). The prognosis in cases with this combination is poor, especially when effusions occur in the late phase of the disease (3). Although a high percentage of cases with pleural involvement are IgA type or IgD type in English language or Japanese literature, respectively (4–6), only seven cases of Bence-Jones myeloma with pleural effusions have been reported (5–11). We present another case of Bence-Jones myeloma with pleural involvement. In addition, we describe the outcome using recombinant α-interferon (IFN-α) combined with oral melphalan-prednisolone (MP) therapy. Treatment with intrapleural IFN-α appeared to be effective and aided the control of myelomatous effusions.

**Case Report**

A 73-year-old female was admitted to our hospital with lumbago and emaciation in October, 1990. Lumbago appeared three months before admission, and had progressed to cause severe disability. She had lost 10 kg of body weight over this three month period. At admission, her body height was 147 cm and weight was 38 kg. Blood pressure was 136/90 mmHg. She appeared markedly pale, but was without systemic lymphadenopathy, hepatosplenomegaly or evidence of purpura. Bilateral breath sound was normal.

The red blood cell count was $228 \times 10^4$/mm$^3$; hemoglobin, 7.3 g/dl; hematocrit, 22.7%; white blood cell count, 3,000/mm$^3$ with 49.2% neutrophils without myeloma cells; and platelet count, 16.3 $\times 10^4$/mm$^3$. Erythrocyte sedimentation rate was 88 mm in the first hour. Blood glucose, liver function and lipid levels were within the normal range. Serum electrolyte concentrations were: Na, 136 mEq/l; K, 3.3 mEq/l; Cl, 99 mEq/l, and Ca, 8.3 mg/dl. Serum BUN was 14 mg/dl; creatinine, 0.6 mg/dl; uric acid, 2.6 mg/dl, and creatinine clearance, 71.6 ml/min. Total serum protein was 6.5 g/dl with 63.5% albumin and 16.5% γ-globulin and without prominent spikes noted on the serum protein electrophoresis. The serum immunoglobulin profile was characterized by decreased levels of all components: IgG, 624 mg/dl; IgA, 27 mg/dl; IgM, 21 mg/dl; IgD, <2 mg/dl, and IgE, 17.4 IU/ml. However, serum immunoelectrophoresis demonstrated Bence-Jones-λ monoclonal proteins (Fig. 1). Despite the presence of serum Bence-Jones protein, urinary protein output was 0.2 g/day and no evidence of Bence-Jones proteinuria was present (Fig. 1). Examination of bone marrow aspirates from the sternum...
Fig. 1. Immunoelectrophoresis of the serum, urine, and pleural effusion. Abnormal precipitation arcs against anti-lambda are clearly noted in the serum and pleural effusion (arrows), but not in the urine. N: normal control, P: patient, A-HWS: anti-human whole serum, A-K: anti-kappa, A-L: anti-lambda.

revealed nucleated cells ($38 \times 10^4$/mm$^3$) with 94.8% immature plasma cells.

Chest radiographs revealed small bilateral pleural effusions (Fig. 2). Computed tomography demonstrated disseminated pleural nodular lesions in addition to pleural effusion. There was no evidence of pulmonary parenchymal lesions or malignant bone destruction (Fig. 2). Skull radiographs also evidenced no osteolytic lesions. X-ray films of the spine and pelvis revealed marked diffuse osteoporosis and L$1$–L$5$ compression. A bone scan showed abnormal radioisotope accumulations in Th$11$ and L$1$–L$5$.

Thoracentesis yielded straw-colored fluid with a specific gravity of 1.030, total protein: 4.2 g/dl, lactate dehydrogenase: 1,148 IU/l, ADA: 35.3 IU/l, CEA: 0.5 ng/ml, SCC: 0.6 ng/ml, NSE: 23.1 ng/ml. Fluid cytology bilaterally revealed numerous immature plasma cells (Fig. 3). Bence-Jones protein was also detected in the pleural fluid by immunoelectrophoresis (Fig. 1).

Clinical course (Fig. 4)
The patient was treated with oral melphalan (6 mg) and prednisolone (30 mg) daily for 4 days, every 4–8 weeks. In addition, IFN-α (300 $\times 10^4$ unit) was administered intramuscularly 3 times a week. The right pleural
effusion was noted to have increased 2 weeks after the onset of systemic treatment (Fig. 5). The effusion was drained and IFN-α (300 × 10^6 unit), dissolved in 10 ml of saline with 1 ml of xylocain, was administered intrapleurally. The patient suffered a high fever for several days, but experienced no chest pain. A small left pleural effusion was drained. This procedure was complicated by an iatrogenic pneumothorax which was successfully reduced. The effusion was subsequently controlled by pleural adhesion therapy. The right pleural effusion gradually decreased and disappeared within 3 weeks, hence, no further treatment with intrapleural IFN-α was initiated (Fig. 5). The patient experienced a gradual resolution of lumbago and anorexia, and experienced an almost complete resolution of her physical disability after 2 courses of therapy. Bence-Jones protein has not been detected in the serum and serum immunoglobulin has returned to within the normal range since the completion of 2 courses of therapy. She has been doing well for 10 months.

**Discussion**

Common causes of pleural effusions in multiple myeloma include: congestive heart failure due to a hyperviscosity or amyloidosis, renal failure, pulmonary embolism due to hyper coagulable state or plasma cell embolization, secondary neoplasm, infection, chylothorax, and bleeding (2, 3, 12, 13). In contrast, pleural effusion due to myeloma cell infiltration is rare. Since pleural effusion due to cell infiltration unrelated cases in multiple myeloma may be rich in monoclonal immunoglobulins,
the presence of myeloma cells in the pleural fluid is necessary to diagnose pleural involvement (5). Klintzer et al (2) reviewed 958 cases of multiple myeloma of which only 8 (0.8%) evidenced pleural involvement. To our knowledge, 32 cases and 47 cases of myelomatous pleural effusion have been reported in the English language and Japanese literature, respectively (5, 6). Bence-Jones myeloma with pleural involvement is reported in only 3 English literature cases and 4 Japanese literature cases (5–11). This is the eighth documented case of Bence-Jones myeloma. In this case, λ type Bence-Jones protein was noted in the serum, but not in the urine. Bence-Jones proteinemia without Bence-Jones proteinuria may be attributable to disturbed renal clearance or to polymerized Bence-Jones protein in the serum (14, 15). It is also possible that the amount of Bence-Jones protein in the serum was so small that it was almost completely reabsorbed at the renal tubule.

It is postulated that myelomatous effusion results from extension from adjacent skeletal or parenchymal plasmacytoma into the pleural space, or by direct implantation into the pleura (2, 16). In this case, no osteolytic lesions in the sternum or ribs and no pulmonary involvement was evident by radiography. However, computed tomography revealed the presence of a pulmonary mass on the right side, and, moreover, a bone scan showed abnormal accumulations in the vertebrae. These results indicate that the myelomatous effusion may have been due to extension from adjacent skeletal structure into the pleura.

IFN-α therapy has been reported to be an effective treatment for multiple myeloma (17–20). Although, as an induction therapy agent, IFN-α is less useful than an alkylating agent, IFN-α is thought to maintain remission by suppressing the clonogenic growth of myeloma cells (20–22). In this case, we combined IFN-α with MP therapy. As described above, the presence of myelomatous pleural effusion has been reported to indicate a poor prognosis with survival usually less than four months (3). Our therapy is successful in maintaining remission for 10 months. However, further observation is needed to determine whether this therapy significantly prolongs survival in this patient.

Several investigators have reported on the effect of intrapleural administration of IFN-α (23, 24). Oda et al (24) postulated that a high density of IFN-α could reach myeloma cells in pleural effusions via intrapleural injection. Waddell and Waddell (25) have proposed that the production of large quantities of immunoglobulin by myeloma cells, which increases the colloid osmotic pressure of the pleural fluid, may result in the development of myelomatous effusion. They have demonstrated that successful systemic chemotherapy can induce a decrease in pleural effusion with an associated decrease in serum protein levels. Shoenfeld et al (26) also have reported the disappearance of pleural effusions following treatment with oral cyclophosphamide. In contrast, Iannitto et al (27) have reported in a patient refractory to systemic therapy who received intrapleural adriamycin, the pleural effusions disappeared with a subsequent marked reduction in pleural fluid paraprotein and myeloma cells. In this case, the right pleural effusion, which increased after a course of systemic therapy, resolved following intrapleural administration of IFN-α and has not recurred. We were therefore unable to determine whether the characteristics of the pleural effusion changed with IFN-α therapy. Although the evaluation of systemic therapy for pleural effusions may be premature, it is possible that intrapleural administration of IFN-α, either alone or in combination with systemic therapy, is effective in the management of myelomatous pleural effusions.

References

Bence-Jones Myeloma with Pleural Effusion