症例報告

The characteristics of myelomatous pleural effusion (MPE) as a rare complication：a case and review of the literature

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Key words：Multiple myeloma (MM) —— myelomatous pleural effusion —— kappa and lambda —— Durie and Salmom classification —— renal dysfunction

Abstract

We reported a patient with multiple myeloma who developed myelomatous pleural effusion (MPE). This patient had nine courses of chemotherapy, and pleural effusion developed after the fourth course. Although administration of several chemotherapeutic agents and intrapleural administration of OK432 were performed, the patient died 4 months after the development of MPE. We analyzed the previous reports to clarify the characteristics of patients who developed MPE.

Introduction

Multiple myeloma (MM) is a malignant proliferation of plasma cells that usually invades the bone marrow but can involve many other organs as well [1]. Extraosseous involvement of myeloma is usually observed in the reticuloendothelial system. Direct pulmonary/pleural involvement or myelomatous pleural effusion (MPE) is rare among the thoracic manifestations of the disease, with an incidence rate of less than 1% [2]. We reported a case in which MPE developed after the fourth course of chemotherapy. Although several courses of chemotherapy and intrapleural infusion of OK432 (Pcibanil) were administered, the patient died 4 months after the development of MPE. We reviewed the previous reports and analyzed 60 cases to clarify the characteristics of patients who developed MPE.

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Case Report

The patient, a 66-year-old female, had developed multiple myeloma. On admission, her red blood cell count was 2440×10^9/l, hemoglobin level was 7.8 g/dl, leukocyte count was 3.0×10^9/l (stab and segmented neutrophiles：39%, metamyelocytes：2%, eosinophils：2%, monocytes：8%, lymphocytes：49%), platelet count was 70.0×10^9/l, lactate dehydrogenase (LDH) was 400IU/l, serum albumin was 4.0g/dl, and C-reactive protein was 0.1mg/dl (normal range is below 0.3mg/dl). Her immunoglobulin G (IgG) count was 5622mg/dl (normal range is from 880 to 1840), and a monoclonal protein of the IgG-k type was detected. The patient's serum β2-microglobulin level was 4.11mg/l (normal range is 0.8-1.9mg/l). A bone marrow aspiration demonstrated normocellular marrow with 59.2% plasma cells. Although the patient was treated with 2 courses of ranimustine (MCNU：70mg/m^2 for 1 day), vindesine sulfate (3mg/m^2 for 1 day), melphalan (8mg/m^2 for 4 days), and prednisolone (60mg/day for 5 days), the effect of this chemotherapy was transient, resulting in increased plasma cells in the bone marrow up to 70.6% thereafter. The chemotherapy was changed to administration of 2 courses of cyclophosphamide (500mg/day for 1 day) and methyl-prednisolone (mPSL：500mg/day for 5 days) and a continuous infusion of vincristine sulfate (0.4mg/day for 4 days) and doxorubicin hydrochloride (9mg/day for 4 days). After the first course of this chemotherapy, IgG level decreased to 1526mg/dl and plasma cells in bone marrow decreased to 12.0%. Thalidomide was subsequently administered to the patient. Pleural effusion was observed 2 days after the administration

of thalidomide （Figure 1），and myeloma cells were found in the pleural effusion (Figure 2). Two courses of a CHOP regimen （cyclophosphamide：750mg/m^2, vincristine：1.4mg/m^2, doxorubicin hydrochloride：50mg/m^2 for 1 day, and prednisolone：60mg/day for 5 days） were therefore administered. Although the myelomatous effusion and plasma cells in bone marrow decreased after the first course of CHOP, MPE and plasma cells in the bone marrow increased after the second course. The MPE was controlled by intrapleural administration of OK432. This was followed by administration of cyclophosphamide (250mg/day for 4 days), etoposide （50mg/day for 7 days), mPSL (500mg/day for 5 days), and thalidomide (100mg/day for 7 days). However, the disease progressed and the patient died of respiratory failure due to lymphangitis brought on by the myeloma cells after 2 courses of cyclophosphamide treatment.

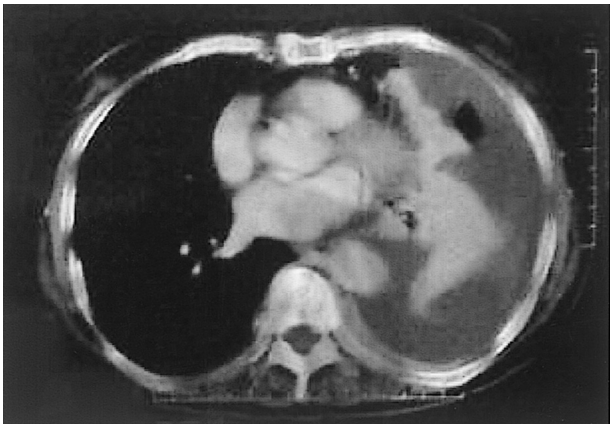

Fig. 1. CT finding of the chest. Pleural effusion developed in the left lung within the wall thickness of the pleura.

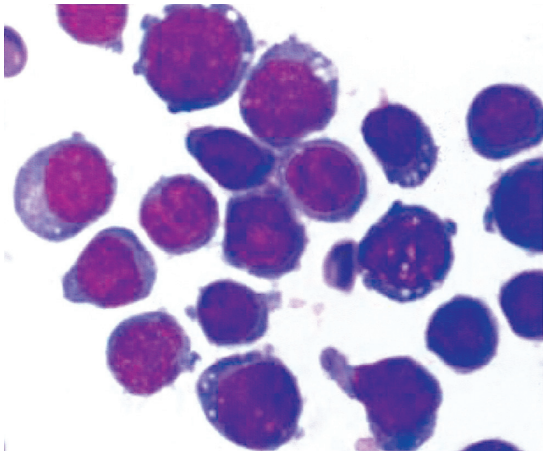

Fig. 2. Cytological finding of the pleural effusion. Abnormal plasma cells appeared in this sample.

Patients and methods

Patients

We searched MEDLINE for reports on MPE patients. Forty-eight reports were found in the listed literature. Among these reports, we selected those in which the development of MPE was clearly mentioned. Sixty-eight such patients were reviewed in this analysis.

Statistical Analysis

Statistical tests were performed with Statview (Brain Power, Calabasas, CA, USA) software, and the data were expressed as mean ± SD or median (range). Statistically significant differences in the analyzed data were determined by the Student's-t test. For all of these tests, a P value of less than 0.05 was considered a statistically significant difference.

Results

Characteristics of MPE patients

The characteristics of the analyzed patients are shown in Table 1. The age of the development of MPE was from 18 to 86 years old, and the median age was 59.8 years old. Many of these patients had IgG or IgA type with plasmacytoma of the lung or pleura, or direct invasion of plasma cells into the pleura, having Stage Ⅲ according to the Durie and Salmom classification. Regarding the distribution of gender, and lambda and kappa chain, there were no significant differences. Almost half of these patients developed left pleural effusion with the first development of the MPE. In these patients, the survival range was from 10 days to 40 months, and the average duration was 5.85 months after the development of MPE. Almost all patients who developed MPE suffered complications of pulmonary plasmacytoma or pleural invasion of multiple myeloma.

Survival analysis by several factors

Survival duration was analyzed by several factors in patients who developed MPE （Table 2). The distribution of the age and gender, the presence or absence of renal dysfunction, and the ratio of

Table 1 Characteristics of patients who developed MPE

Age	59.8(range from 18 to 86 yo)
Gender	
M/F	26/24
Subtype	
IgG	30
IgA	17
IgD	2
IgM	1
LC	5
BJP	2
null	1
lambda/kappa	25/27
Alb	3.56
Stage	
Ⅰ	4
Ⅱ	8
Ⅲ	30
Location of effusion	
Left	26
Right	16
Bilateral	11
Survival	5.85(range from 10 days to 40 months)
Pulmo nary or pleural lesion	
＋/－	42/4

Table 2 MPE and several factors related to survival

	Survival (months)	P
Age		
≧65yo	6.27	0.99
＜65yo	6.29	
Gender		
M	6.68	0.77
F	5.88	
Serum albumin		
≧3.5	3.83	0.23
＜3.5	8.28	
Bone lesion		
Positive	4.55	0.30
Negative	7.13	
Plasma cell in peripheral blood		
Positive	5.58	0.98
Negative	5.66	
Renal dysfunction		
Positive	8.11	0.50
Negative	5.81	
Stage		
Ⅰ＋Ⅱ	9.77	0.039
Ⅲ	4.18	
Local treatment		
Not added	6.71	0.60
added	8.56	

plasma cells in the peripheral blood did not significantly differ in terms of survival duration. Although the patients with renal dysfunction appeared to have longer survival duration than those without renal dysfunction, there was no significant difference. The patients with more than 3.5g/dl serum albumin appeared to have shorter survival duration than those with a lower level. Furthermore, the patients with bone lesion appeared to have shorter survival duration than those without bone lesion. However, no significant differences were observed. The patients at Stage Ⅲ had significantly shorter survival durations than the patients at Stages Ⅰ and Ⅱ (P=0.039). Although additionally local treatment with systemic chemotherapy appeared to induce longer survival duration in MPE patients, there was no significant difference.

Characteristics of MPE by lambda and kappa chain specificity

The survival duration did not significantly differ in terms of the distribution of the lambda and kappa chains, age, gender, the ratio of plasma cells in the peripheral blood, or the existence of bone lesion. Renal dysfunction was more often seen in the patients with MPE composed of a lambda chain (Table 3；P=0.017). Although the patients at Stages Ⅰ and Ⅱ often had MPE composed of a lambda chain, there was no significant difference between them.

Discussion

MPE was a rare complication of multiple myeloma patients [2]. Although several kinds of treatments were administered, the survival duration of the multiple myeloma patients who developed MPE was

Table 3　MPE of characteristics of Lambda and Kappa myeloma

	Lambda	Kappa	P
Age	61.3	59.0	0.59
Gender			
M/F	10/8	12/12	0.73
Location of effusion			
Left	7	10	
Right	7	8	
Bilateral	5	3	
Plasma cell in peripheral blood			
Positive/Negative	3/20	4/15	0.50
Renal dysfunction			
Positive/Negative	8/6	2/11	0.017
Bone lesion			
Positive/Negative	9/6	13/5	0.47
Stage			
Ⅰ	3	1	
Ⅱ	5	3	
Ⅲ	9	15	
Ⅰ＋Ⅱ／Ⅲ	8/9	4/15	0.20
Survival	6.19	5.77	0.88

indeed miserable [26]. The presented case also died of lymphangitis 4 months after the development of MPE in spite of treatments with several chemotherapeutic agents and local administration of OK432.

Then we analyzed the previous literature to clarify the characteristics of the multiple myeloma patients who developed MPE [2-47]. Longer survival duration was observed in the patients at Stages Ⅰ and Ⅱ. Many of the patients who developed MPE were considered to be experiencing the disease progression of multiple myeloma. Although additional local treatment to such patients appeared to induce longer survival duration, this made no significant difference. The average survival duration of the patients with only local treatment was shorter than that of those with systemic chemotherapy (2.92 months for patients with only local treatment). This suggests that local treatment was effective for the control of MPE but that systemic treatment was necessary for further improvement [3, 5, 9, 12, 16-21, 24, 31, 33, 36, 38, 44]. In our analysis of the previous reports, the involvement of $\beta 2$ microglobulin was rarely mentioned. In our analysis, we utilized the serum albumin level at the onset of MPE, which reflects the disease status according to the international score system (ISS) [48]. Although the survival duration appeared to be shorter in the patients with more than 3.5g/dl serum albumin than in those with a lower level, there was no significant difference. Therefore, Durie and Salmon classification may be more suitable for evaluating the prognosis of the patients with MPE than ISS, suggesting that MPE develops in a certain and unique population of the patients with multiple myeloma. However, since ISS includes the data on $\beta 2$ microglobulin in addition to those on serum albumin, we need to examine through a large-scale study whether only serum albumin is sufficient to estimate the prognosis without taking $\beta 2$ microglobulin into account.

In terms of kappa and lambda chain specificity, renal dysfunction was more often seen in the patients with MPE composed of a lambda chain. In general, renal dysfunction was often observed in patients with increased kappa chain [49, 50]. This discrepancy might reflect the changes in the expression of adhesion molecules, thereby causing MPE in the patients with increased lambda chain even at the early stage.

Based on this analysis, Durie and Salmom classification might be suitable for estimating the prognosis of patients with MPE. Although the prognosis of patients with MPE is actually miserable, progress in systemic and local treatment can improve the survival duration of patients with MPE. Further large-scale study is needed to draw a conclusive result.

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