原　著

Cytogenetic analysis in a multiple myeloma patient who developed myelomatous pleural effusion and plasma cell leukemia

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Key words：Multiple myeloma（MM）—— myelomatous effusion —— plasma cell leukemia —— deletion 16 —— cytogenetic analysis

Abstract

We report on a patient with multiple myeloma who developed myelomatous pleural effusion and plasma cell leukemia. After the fourth course of chemotherapy, pleural effusion developed, and plasma cells were observed in peripheral blood after the sixth course of chemotherapy. Homozygous loss of chromosome 16 and monosomy X developed before the fourth course of chemotherapy. In this case, such cytogenetic abnormalities may be related to the myelomatous effusion and leukemic changes in multiple myelomas.

Introduction

Multiple myeloma (MM) is a malignant proliferation of plasma cells that mainly affects bone marrow, but can also involve many other organs [1]. Direct pulmonary, pleural involvement, or myelomatous pleural effusion (MPE) is rare among the thoracic manifestation of the disease, with a frequency of less than one percent [2]. We report a case in which MPE developed after the fourth course of chemotherapy. Plasma cell leukemia (PCL) arose after the sixth course of chemotherapy when the number of plasma cells in the bone marrow had stabilized. A cytogenetic analysis revealed the homozygous loss of chromosome 16 and monosomy X, that developed before the fourth course of chemotherapy. This cytogenetic abnormality was also seen in plasma cells in the peripheral blood.

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Case Report

The patient, a 66 year-old woman, had developed multiple myeloma. On admission, her red blood cell count was 244×10^{10}/l, her hemoglobin level was 7.8 g/dl, her leukocyte count was 3.0×10^{9}/l (stab and segmented neutrophiles：39%, metamyelocytes：2%, eosinophils：2%, monoocytes：8%, lymphocytes：49%), her platelet count was 7.0×10^{10}/l, her lactate dehydrogenase (LDH) was 400IU/l, and her C-reactive protein was 0.1mg/dl (normal range is below 0.3mg/dl). In addition, her immunoglobulin G(IgG)count was 5,622mg/dl (normal range is from 880 to 1,840), and a monoclonal protein of the IgG-k type was detected. The patient's β2-microglobulin level was 4.11mg/L (normal range from 0.8−1.9mg/L), and a bone marrow aspiration demonstrated normocellular marrow with 59.2% plasma cells (Figure 1A).

The patient was first treated with two courses of MCNU-VMP consisting of ranimustine (MCNU：70 mg/m^2 for one day), vindesine sulfate (3 mg/m^2 for one day), melphalan (8 mg/m^2 for four days), and prednisolone (60mg/body for five days). Serum IgG levels decreased temporarily but elevated again after the second course of MCNU-VMP. Plasma cells in the bone marrow increased to 70.6%. The patient was then administered two courses of modified cyclo-VAMP containing cyclophosphamide (500mg/body for one day) and methyl-prednisolone (mPSL：500mg/body for five days), and a

continuous infusion of vincristine sulfate (0.4mg /body for four days) and doxorubicin hydrochloride (9 mg/body for four days). After the first cyclo-VAMP was administered, the IgG level decreased to 1,526mg/dl and plasma cells in the bone marrow decreased to 12% (Figure 1B). However, serum IgG levels and plasma cells in the bone marrow increased after the second course of cyclo-VAMP. The patient was subsequently administered thalidomide. Pleural effusion was observed two days after administration of thalidomide(Figure 2), and myeloma cells were found in the pleural effusion (Figure 1C). Two courses of a CHOP regimen (cyclophosphamide：750mg/m^2, vincristine：1.4mg/m^2, doxorubicin hydrochloride：50mg/m^2 for one day, and prednisolone：60mg/body for five days) were performed on the patient. Results showed that although the myelomatous effusion and plasma cells in the bone marrow decreased after the first course of CHOP, MPE and plasma cells in bone marrow increased after the second course. Plasma cells then appeared in the peripheral blood (Figure 1D). Consequently, the patient was administered modified T-CED (cyclophosphamide：250mg/body for four days, etoposide：50mg/body for seven days, mPSL：500 mg/body for five days, and thalidomide：100mg/body for seven days). After this treatment, MPE and plasma cells in the peripheral blood decreased slightly. The patient died of respiratory failure due to MPE and lymphangitis brought on by the myeloma cells after two courses of cyclophosphamide.

A cytogenetic analysis upon admission revealed near-tetraploid abnormality in the bone marrow (Figure 3A)；these abnormality changed into triploid patterns, and homozygous loss of chromosome 16 and monosomy X were noted after the third course of chemotherapy (Figure 3B). MPE developed after the chromosomal deletion was confirmed. In addition, plasma cells appeared in the peripheral blood after the number of myeloma cells in the bone marrow was stabilized. Similar triploid abnormalities in chromosomes were found in the peripheral blood (Figure 3C).

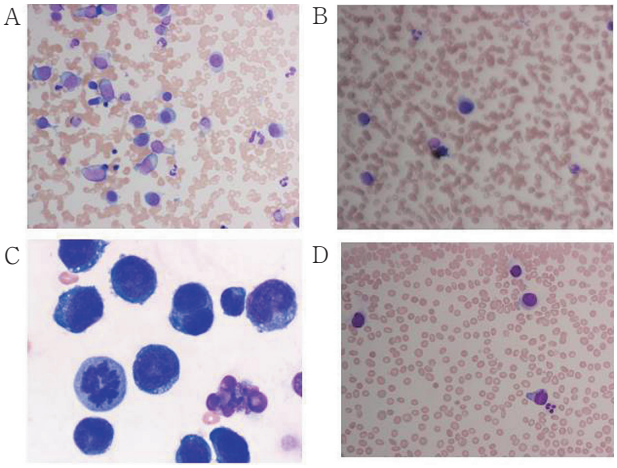


Fig. 1. Cytological and Pathological findings. A. Bone marrow aspiration of the patient on admission. The sample indicated 60% plasma cells. B. Bone marrow aspiration of the patient after two courses of cyclo-VAMP. Plasma cells have decreased to 12% in this sample. C. The cytological findings of the pleural effusion. Abnormal plasma cells appeared in this sample. D. Peripheral blood sample after CHOP therapy. Plasma cells appeared in this sample.

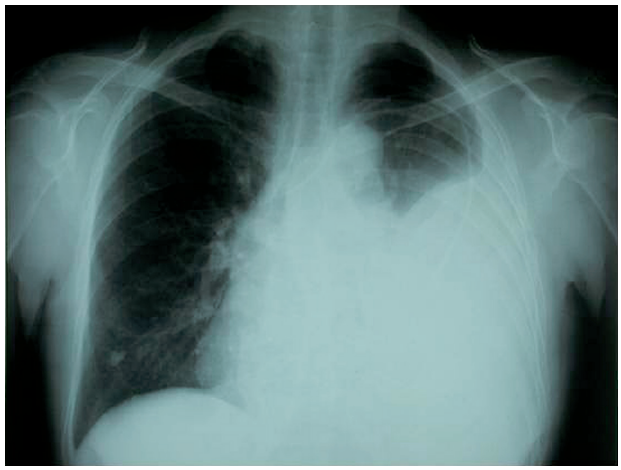
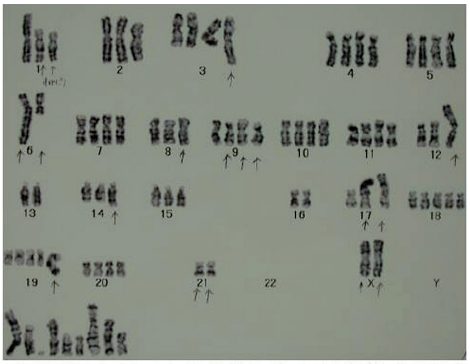
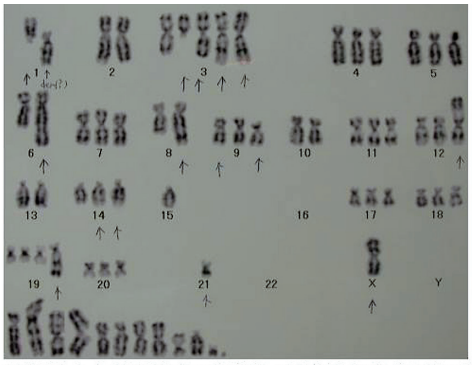


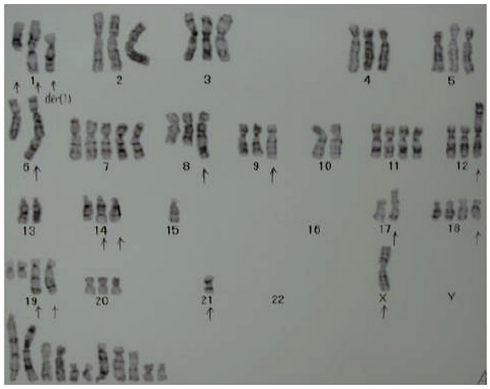
Fig. 2. Pleural effusion developed in the left lung two days after administration of thalidomide.



82, -X, -X, add(X)(p22)x2, -1, -1, -1, -2, der (3)t (1;3)(p13; q21), -6, -6, del (6)(q?), der (6)t(1;6)(q12; q27), -8, add(8)(p11), add(9)(p11), add(9)(p13), der(9;21)(q10; q10), -12, add(12)(p13), -13, -13, -14, add(14)(q32), -15, -16, -16, -17, add(17)(p11), der(17)t(1; 17)(q21; p13), +18, +add(19)(q13), -21, -21, add(21)(p11)x2, -22, -22, -22, -22, -22,der(?)t(?; 1)(?; 21)x2, +9mar



66, **-X, -X,** add(X)(p22), -1, -1, add(1)(q11), -2, +add(3)(q11), +add(3)(q11), der (3)t (1; 3)(p13; q21), der(3)add(3)(p11)t(1; 3), -6, add(6)(q27), -8, add(8)(q22), add(9)(p11), add(9)(p13), -10, add(12)(p13), -13, add(14)(q32)x2, -15, -15, **-16, -16, -16,** +add(19)(q13), -21, -21, add(21)(p11), -22, -22, -22, der(?)t(?; 1)(?; 21), +12mar



69, **-X, -X,** add(X)(p22), -1, add(1)(q11), add(1)(q21), -6, der(6)t(1; 6)(q12; q27), +7, +7, add(8)(q22), der(9)add(9)(p11)add(9)(q22), -10, +11, add(12)(q13), -13, add(14)(q32)x2, -15, -15, **-16, -16, -16,** -17, , add(17)(p11), +add(18)(q21), +add(19)(q13), +add(19)(q13), -21, -21, add(21)(p11), -22, -22, -22, der(?)t(?; 1)(?; 21), +11mar

Fig. 3. Cytogenetic analysis. A. Cytogenetic analysis on admission. Diploid abnormality is indicated in this figure. B. Cytogenetic analysis when mylomatous pleural effusion developed. New abnormalities in the homozygous loss of chromosome 16 and monosomy X appeared. C. Cytogenetic analysis when plasma cell leukemia developed. The homozygous loss of chromosome 16 and monosomy X was also observed.

Discussion

Pleural effusion in MM occurs in about six percent of patients. However, except for pleural effusion due to heart failure, secondary amyloidosis, pulmonary embolism, chronic renal failure, or secondary neoplasm, MPE are complicated in less than one percent [2]. Although MPE has been reported by several investigators, cytogenetic analysis of myeloma cells was not performed [3-5]. In this case, pleural effusion developed when the plasma cells in the bone marrow had been brought under control.

In this patient, the homozygous loss of chromosome 16 was determined in bone marrow samples prior to MPE development. Thus, the occurrence of MPE might be associated with the homozygous loss of chromosome 16. In addition, the appearance of plasma cells in the peripheral blood might also be related to the MPE.

Cytogenetic results in patients with MM and PCL have been reported by several investigators, with such results as the following: monosomy 13, gain of chromosome 18, the loss of chromosome 16 in MM, and monosomy X in PCL [6,7]. These chromosomal abnormalities might be connected to the changes in the expression of adhesion molecules. In the case described here, a gain of chromosome 18 was detected in the bone marrow before the first administration of chemotherapy, but PCL did not develop during that first course. It is, therefore, unlikely that the gain of chromosome 18 is related to the development of PCL in this case. As mentioned above, The near-tetraploid abnormality was detected in the bone marrow on admission. The chemotherapeutic agent was effective at the beginning of treatment, but only for a short duration, suggesting that this tetraploid chromosomal abnormality might cause resistance to the chemotherapeutic agent. In fact, Hata et al. have reported that drug refractoriness was observed in a patient with hyperdiploid myeloma [8].

The homozygous loss of chromosome 16 and monosomy X arose before the development of MPE, and after the appearance of plasma cells in the peripheral blood, when the myeloma cells in the bone marrow were brought under control in

response to treatment, a similar triploid abnormality appeared. This suggests that the appearance of myeloma cells in the peripheral blood coincided with the development of MPE. Furthermore, the homozygous loss of chromosome 16 and monosomy X were also thought to be associated with the development of the MPE, although other cytogenetic abnormalities may interact with these two abnormalities

Several investigators have established myeloma cell lines from MPE [9-11], with the cytogenetic abnormalities in these cell lines differing from each other [9,10]. These facts suggest that the cause of cytogenetic abnormalities in the development of the MPE is still controversial, and further studies are necessary to clarify these phenomena.

Although the treatment of MPE has been performed by systemic chemotherapy, radiation, and intrapleural chemotherapy, prognosis of the MPE has yielded disappointing results: almost all patients who developed MPE have died in four months or less [9-14]. In spite of administering several systemic chemotherapies, our presented case also died 3.5 months after the development of MPE. In light of such results, we consider that the management of MPE should include both systemic and local therapy.

Based on our experience, it appears that the loss of genes on chromosomes 16 and X might play an important role in the development of MPE.

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