

## Case Report

# Multiple myeloma presenting with pleural effusion and extramedullary masses and harboring a novel chromosomal abnormality, t(1;5)(p22;q31): a case report

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**Abstract:** We report the case of a 70-year-old male who developed multiple myeloma involving myelomatous pleural effusion and extramedullary masses. Chemotherapy consisting of bortezomib, oral cyclophosphamide, and dexamethasone resulted in the disappearance of the pleural effusion and masses. Although patients with myelomatous pleural effusion tend to have a poor prognosis, bortezomib-containing chemotherapy might be a useful treatment for myelomatous pleural effusion as well as extramedullary myeloma. Besides, the cells in the pleural effusion harbored a novel chromosomal aberration, t(1;5)(p22;q31). The further accumulation of cases with this translocation is necessary to enable its impact on tumorigenesis to be evaluated.

**Keywords:** Multiple myeloma, myelomatous pleural effusion, t(1;5)(p22;q31), bortezomib

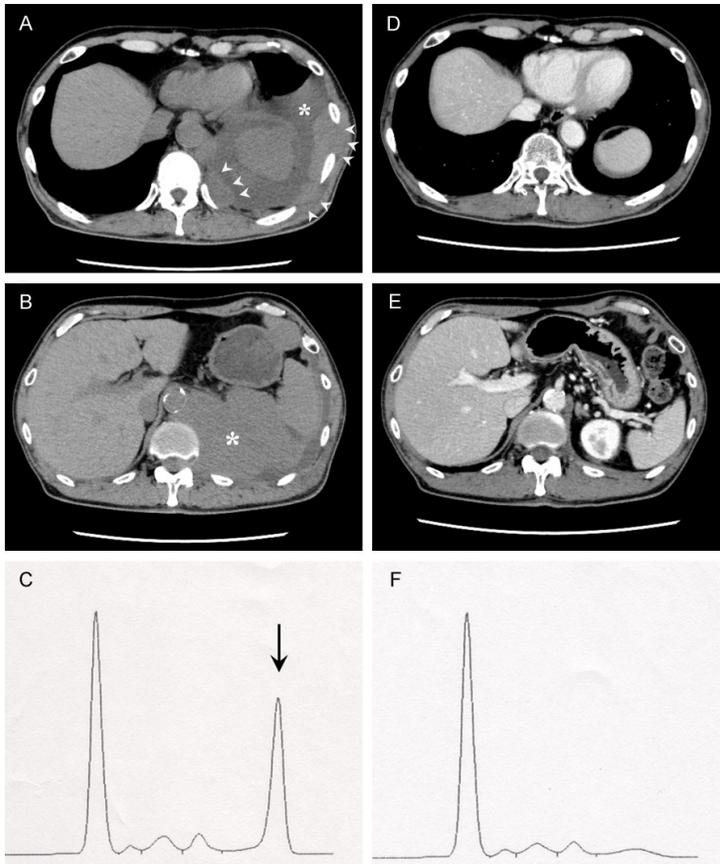
### Introduction

Multiple myeloma (MM) is a plasma cell neoplasm that is associated with the detection of M-protein in serum and/or urine. MM is mostly confined to the bone marrow; however, a subset of MM patients develops extramedullary myeloma (EMM), which is characterized by the presence of clonal plasma cells outside of the bone marrow. The most common sites of EMM involvement are the liver, skin, central nervous system, pleural effusions, kidneys, lymph nodes, and pancreas [1]. Myelomatous pleural effusion (MPE) is relatively rare, and patients who develop MPE have a poor prognosis [2].

Here, we present a case of MM in which the tumor cells harbored a novel translocation, t(1;5)(p22;q31). This case involved pleural effusion and extramedullary masses and was successfully treated with chemotherapy involving bortezomib, oral cyclophosphamide, and dexamethasone.

### Clinical summary

A 70-year-old male was referred to our hospital due to dyspnea on effort, coughing, and left abdominal pain. He was a current smoker, and his medical history included diabetes mellitus, which was being treated with oral acetohexamide alone (hemoglobin A1c level: 7.0%). He had no history of trauma, surgery, or bone fractures. On admission, a physical examination revealed several masses in the chest wall, and quieter breath sounds were heard in the left thorax during a chest examination. The patient's initial laboratory findings included a white blood count of 6200/ $\mu$ L without atypical cells, a hemoglobin concentration of 14.2 g/dL, a platelet count of  $17.2 \times 10^4$ / $\mu$ L, a total protein level of 8.2 g/dL, and an albumin level of 3.7 g/dL. The patient's serum levels of electrolytes, bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, and C-reactive protein were within the normal ranges. Tests for hepatitis B virus antigen,



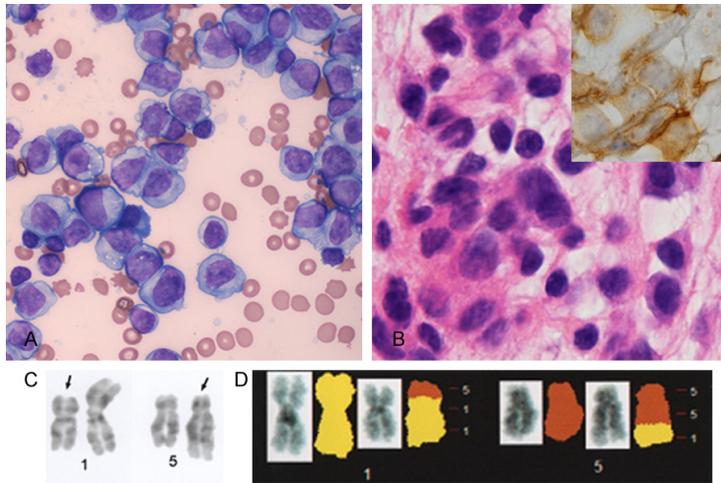
**Figure 1.** (A, B) Computed tomography revealed left pleural effusion (asterisk), pleural masses (arrowheads) (A), and a mass in the retroperitoneum (asterisk) (B). (C) Serum electrophoresis performed at diagnosis showed marked M-protein (arrow). (D-F) After three courses of chemotherapy, the pleural effusion and masses had disappeared (D, E), and the patient's M-proteinemia had almost normalized (F).

hepatitis C virus antibody, and human immunodeficiency virus antigen were negative. The results of a urine dipstick test were indicative of proteinuria, but no glycosuria or hematuria was detected. A chest X-ray showed left-sided pleural effusion and mass shadows that were indicative of masses in the chest wall. Computed tomography (CT) revealed left-sided pleural effusion and abnormal masses in the pleura, right iliopsoas muscle, and retroperitoneum (Figure 1A, 1B). Thoracentesis was performed to investigate the etiology of the patient's condition. His left-sided pleural fluid was slightly bloody and hypercellular (4800/ $\mu$ L) and exhibited a total protein concentration of 5.9 g/dL, a lactate dehydrogenase concentration of 299 IU/L, an adenosine deaminase concentration of 27.8 IU/L, and a specific gravity value of 1.042. On the other hand, a polymerase chain

reaction test for *Mycobacterium tuberculosis* produced a negative result. A cytological examination of the pleural fluid revealed extensive tumor cell infiltration (by medium- to large-sized cells displaying nuclear atypia, fine chromatin, and basophilic cytoplasm; some of the cells had perinuclear halos) (Figure 2A). Surface marker analysis demonstrated that the abnormal cells expressed CD38 (58.1%). The cells' positivity rates for other antigens were as follows: CD19: 52.6%, CD56: 1.1%, mitochondrial pyruvate carrier 1: 34.5%, CD45: 84.2%, CD49e: 0.8%, CD138: 81.0%, CD20: 0.5%, cytoplasmic immunoglobulin (cylg)-kappa: 1.7%, cylg-lambda: 77.8%. He underwent a percutaneous biopsy of the pleural mass, which demonstrated a densely cellular tumor composed of CD38-positive plasma cells (Figure 2B). A chromosomal analysis of the abnormal cells detected in the pleural effusion revealed the following karyotype: 46,XY,t(1;5)(p22;q31),inv(2)(p13q33)c[4]/46,XY,t(1;5)(p22;q31),inv(2)(p13q33)c,der(13)t(13;19)(q14;?) [6], and spectral karyotyping (SKY) showed the same karyotype (Figure 2C, 2D). Based on

the detection of a breakpoint at 1p22, the formalin-fixed paraffin-embedded pleural biopsy specimen was also subjected to interphase fluorescent *in situ* hybridization analysis; however, no rearrangement was detected using the *BCL10* (1p22) break-apart probe (Vysis LSI *BCL10* Dual Color Break Apart Rearrangement Probe, Abbott Molecular Inc., IL, USA; data not shown).

The proliferation of CD38-positive cells was suggestive of a plasma cell neoplasm. Hence, we performed a further laboratory examination, which revealed the following values: IgG: 3989 mg/dL, IgA: 42 mg/dL, IgM: 103 mg/dL,  $\beta$ 2-microglobulin: 2.4 mg/L, free light chain-kappa: 2.3 mg/L (reference range, 3.3-19.4 mg/L), free light chain-lambda: 662.0 mg/L (reference range, 5.7-26.3 mg/L). Serum protein immuno-



**Figure 2.** A: Pleural fluid cytology (May-Giemsa stain,  $\times 630$ ). B: Pathological examination of the pleural biopsy specimen showing plasma cell infiltration (hematoxylin-eosin stain,  $\times 1000$ ; CD38, inset). C: G-banded partial karyogram showing the t(1;5)(p22;q31) translocation. D: Spectral karyotyping of the patient's metaphase spread after spectrum-based classification (left, counterstained with 4',6-diamino-2-phenylindole dihydrochloride; right, SKY).

electrophoresis showed a marked M-protein (IgG-lambda) fraction, and a urine test was also positive for Bence-Jones protein. Unexpectedly, bone marrow aspiration did not obtain any evidence of plasma cell proliferation ( $<1\%$ ), and the examined cells did not exhibit any chromosomal abnormalities other than inv(2)(p13q33) c. Although no bone marrow plasmacytosis was seen, both M-protein (**Figure 1C**) and Bence-Jones protein had been detected; hence, a diagnosis of MM was made according to the criteria outlined by the International Myeloma Working Group [3].

The patient was administered chemotherapy involving  $1.3 \text{ mg/m}^2$  intravenous bortezomib on days 1, 8, and 15; 50 mg oral cyclophosphamide every day; and 40 mg dexamethasone on days 1, 8, and 15 per 4 weeks. After 3 courses of chemotherapy, CT showed that the pleural effusion and the masses in the iliopsoas muscle, retroperitoneum, and chest wall had disappeared (**Figure 1D, 1E**), and his abdominal pain, dyspnea, and cough were also resolved. In addition, the patient's free light chain levels had normalized (free light chain-kappa: 7.0 mg/L, free light chain-lambda: 16.0 mg/L) as had his serum M-protein level (**Figure 1F**). At 7 months after initial diagnosis, there was no evidence of relapse. The patient is currently being followed-up as an outpatient.

## Discussion

Extramedullary disease is rare in patients with MM; i.e., it is found in 6-8.3% of patients during baseline staging performed at the time of the diagnosis of MM [4-6]. In addition, EMM is seen in about 10-30% of patients with advanced or relapse MM [1, 7]. Among cases of EMM, MPE is considered to be extremely rare; i.e., it is estimated to occur in  $<1\%$  of MM patients [8]. To date, only around 100 cases of MPE have been reported [9]. In a recent study, it was most commonly found on the left side (40.4%), in the IgG-type of MM (40.4%), and during the late stage of the disease [2]. Our patient also exhibited some of these typical characteristics, e.g., the MPE occurred on the left side and the patient had IgG-type MM.

However, regarding the timing of disease onset, it seems to be rare for MPE to be detected at the time of the initial diagnosis. Furthermore, a diagnosis of systemic MM was made in the present case because of the detection of M-protein in both the patient's urine and serum. However, plasma cell proliferation was not detected in the patient's bone marrow, and only extramedullary disease was seen. Although plasma cells are detected in the bone marrow in most MM patients, it is suggested that several diagnostic methods such as pleural cytology, surface marker analysis, and pleural pathological examinations, might be useful for obtaining an accurate diagnosis in cases of suspected typical MM that do not involve plasma cell proliferation in the bone marrow.

Concerning chromosomal abnormalities, the t(1;5)(p22;q31) translocation found in our patient has never been reported before according to the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer [10]. In our case, with the exception of the normal variant inv(2)c, t(1;5)(p22;q31) was the only chromosomal abnormality detected in the stem line. Hence, it seems that the t(1;5)(p22;q31) plays a crucial role in the primary development of MM. Generally, in most newly diagnosed symptomatic cases of MM the neoplastic cells are hyperdiploid with multiple triso-

mies, or hypodiploid and possess one of several types of immunoglobulin heavy chain translocations [11]. In our case, no chromosome number aberrations or translocations involving the immunoglobulin heavy chain locus were seen, which seems to be relatively rare. Although we could not perform detailed genetic mutational evaluations (other than of the *BCL-10* gene) in the present case due to a lack of specimens, more case studies are needed to evaluate the genetic mutations responsible for this translocation.

Finally, it has been reported that the mean survival period after the diagnosis of MPE is approximately 4 months [2]. However, bortezomib was recently reported to be effective against extramedullary plasmacytomas [12]. In addition, it was suggested that bortezomib is effective against cases of EMM in which other agents, including immunomodulatory drugs; i.e., thalidomide, are not effective. Moreover, Zhong et al. reported that chemotherapy involving bortezomib prolonged the overall survival of MPE patients to 11.7 months [9]. Although the follow-up period was short in the present case (7 months), the administration of chemotherapy involving bortezomib resulted in symptom relief and the disappearance of the patient's pleural effusion and masses. Therefore, we consider that a therapeutic strategy that includes bortezomib therapy might be suitable for patients like ours, especially those with MPE.

#### Disclosure of conflict of interest

None.

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