A case of simultaneous presentation of symptomatic PCM and MDS unrelated to prior chemotherapy

TO THE EDITOR: As chemotherapy for the treatment of plasma cell myeloma (PCM) includes alkylating agents, the incidence of therapy-related myeloid neoplasms such as acute myeloid leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasm due to prior PCM chemotherapy has increased. Several studies reported the mutagenic effect of some PCM treatment regimens on the development of MDS [1-3]. By contrast, cases with simultaneous presentation of PCM and MDS unrelated to prior chemotherapy are far less frequently observed than cases with MDS related to prior chemotherapy [4-6]. A recent study reported that in a period of 14 years, only 14 cases of monoclonal gammopathy and MDS unrelated to chemotherapy or radiotherapy were reported, representing 12 cases of monoclonal gammopathy of undetermined significance (MGUS) and 2 cases of smoldering myeloma (SM) [7]. We report a case of simultaneous presentation of symptomatic PCM and MDS unrelated to prior chemotherapy.

CASE
An 80-year-old woman was admitted to our hospital because of chest pain that developed 1 day prior to admission. She had been treated for bronchial asthma with a bronchodilator and leukotriene antagonist for 2 years but had no medical history related to hematologic malignancy. The patient’s hemogram results at admission were as follows: white blood cell count, 0.95×10^9/L; hemoglobin level, 8.0 g/dL; mean corpuscular volume, 105.9 fl; and platelet count, 29.0×10^9/L. The patient’s biochemical test results at admission were as follows: serum protein level, 6.8 g/dL; serum albumin level, 2.8 g/dL; serum creatinine level, 1.54 mg/dL; serum calcium level, 7.4 mg/dL; and serum lactate dehydrogenase level, 719 IU/L. In the examination of a peripheral blood smear, pancytopenia with rouleaux formation was observed. Bone marrow aspirates showed hypocellular marrow without an increase in the number of myeloblasts but showed increased infiltration of plasma cells at a frequency of 14.9% (Fig. 1A). In addition, megakaryocytic dysplasias such as separated nuclei (Fig. 1A) and hypolobulated nuclei (Fig. 1B and C) were found, accounting for 30% of the total number of megakaryocytes. Erythroid dysplasias such as binucleation and delayed mitosis were also found (Fig. 1C and D), as well as mild granulocytic dysplasias such as hypo-segmentation, accounting for 15% and 10% of the total numbers of erythroid and granulocytic lineage cells, respectively. Examination of a bone marrow biopsy specimen (Fig. 1E) revealed 35% cellular marrow with diffuse infiltration of plasma cells in the immunohistochemical stain for CD138 expression (DAKO, Glostrup, Denmark; Fig. 1F).

Both serum and urine immunofixation analyses using Hydragel IF K20 kit (Sebia, Cedex, France) were performed, and the results showed the presence of monoclonal gammopathy of IgA and lambda type. The subsequently performed serum electrophoresis using Capillaries Protein(E) 6 kit (Sebia, France) showed the presence of monoclonal gammopathy accompanied by M-peaks of 1.27 g/dL. All radiological evaluation results did not show definite evidence of osteolytic lesion. The results of a subsequently performed karyotype analysis showed 46,XX, del(20)(q11.2)[15]/46,XX[5], indicating the presence of del(20)(q11.2) clone, at a frequency of 75%. Fluorescence in situ hybridization analysis results showed nuc ish(D20S108X1)[156/200], indicating the presence of heterozygous 20q12 deletion, at a frequency of 78%. As the patient showed pancytopenia accompanied with multilineage dysplasia, MDS-related chromosomal abnormality, and monoclonal gammopathy with an increase in serum creatinine level, she was finally diagnosed with the simultaneous presentation of symptomatic PCM and MDS and refractory cytopenia with multilineage dysplasia (RCMD) that were unrelated to prior chemotherapy. After the diagnosis, she developed gram-negative septicemia and died 8 days after the admission.

DISCUSSION
Our case had similar features regarding the type of MDS-related chromosomal abnormality as those of cases reported in previous studies. Most MDS cases accompanied by MGUS/SM showed a low risk of chromosomal abnormal-
Fig. 1. Bone marrow findings showing both features of plasma cell myeloma and myelodysplastic syndrome. The arrows indicate megakaryocytes with separated (A) and hypolobulated nuclei (B, C), and erythroblasts with binucleation (C, lower side) and delayed mitosis (D), respectively. Bone marrow biopsy revealed diffuse infiltration of plasma cells (E) that were CD138 positive (F).

ities, and our case also showed del(20)(q11.2), which is a well-known chromosomal abnormality related to good prognosis in MDS [7]. In addition, our case did not show any history of prior chemotherapy or radiotherapy, which supports the occurrence of simultaneous MDS and symptomatic PCM. Notably, compared with previously reported cases, our case presented unique clinical features that are worth reporting [7]. Our case developed symptomatic PCM, which has not been reported yet, and showed poor prognosis.

In conclusion, we report a rare case of simultaneous pre-
sentation of symptomatic PCM and MDS RCMD unrelated to prior chemotherapy or radiotherapy. A more extensive study would be required to investigate the clinical characteristics and outcomes in patients with such a condition.

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REFERENCES

Regaining the response to erythropoietin following azacitidine in chronic myelomonocytic leukemia previously evolved from refractory anemia

TO THE EDITOR: In a previously published issue of the Journal, we reported an unusual case of chronic myelomonocytic leukemia (CMML) type 2 (CMML-2) that evolved from refractory anemia (RA) [1]. The complete development of CMML was preceded by the loss of response to epoetin alpha (EPO). EPO had allowed the patient to maintain the transfusion independence (TI) for 7 years until then. The patient received azacitidine, achieving complete remission (CR) of CMML-2 after 6 treatment courses. However, the TI was observed after 2 cycles of hypomethylating therapy despite the persistence of myelodysplastic features. The optimal response to azacitidine in this patient was in line with that reported by our group earlier [2]. Moreover, the limited clinical efficacy of azacitidine in transfusion-dependent and erythropoiesis-stimulating agent (ESA)-resistant, low and intermediate-1 risk myelodysplastic syndrome (MDS) has been recently outlined [3]. Therefore, we could speculate that several and different biological components and pathogenic mechanisms, stemming from different patterns of response to distinct therapeutic agents, may be responsible for the myelodysplasia and the resulting clinical phenotype. These findings might be observed more easily during treatment with hypomethylating agents as these agents induce downstaging of high-risk MDS to low-risk MDS.

Here, we report the updated follow-up of the clinical course of our patient, wherein we observed a dynamic evolution of MDS clones that showed different responses to azacitidine and EPO. The response to EPO was likely related to the persistence of RA clones that re-emerged despite azacitidine. After the achievement of the TI and the CR following the second and the sixth azacitidine courses, respectively, the patient continued to receive hypomethylating therapy as maintenance. However, after the fourteenth course, preceded by several weeks in which the patient complained of profound weakness and fatigue [4], progressive anemia (hemoglobin ∼7.0 g/dL) requiring red blood cell (RBC) transfusions was noted. Therefore, the patient was reevaluated in the light of the suspicion of a loss of response to azacitidine and evolution to acute myeloid leukemia. However, examination of the bone marrow (BM) showed the disappearance of blast cells and a marked reduction of monocyes in a MDS framework, which was characterized by trilineage dysplasia and erythroid predominance with the features of ineffective erythropoiesis, as observed at the onset of MDS when the patient was diagnosed with RA [1]. According to its disease-modifying effects in MDS,