Development of multiple myeloma after 15 years of treatment for polycythaemia vera and successful treatment using bortezomib: A case report

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Abstract
Multiple myeloma (MM) and polycythaemia vera (PV) rarely coexist; the clinical manifestations and treatment of this coexistence have not been described. An 81-year-old woman developed MM 15 years after undergoing PV treatment and was successfully treated using bortezomib. Herein, we share our experience of treating MM under such unusual conditions.

KEYWORDS
bortezomib, multiple myeloma, myeloproliferative neoplasia, polycythaemia vera

1 | INTRODUCTION

The coexistence of multiple myeloma (MM) and polycythaemia vera (PV) was first described by Lawrence and Rosenthal in 19481; however, subsequent cases have been sporadically reported. Maeda and Abraham reported on patients with coexisting MM and PV, comprehensively summarizing 11 cases reported before 19842; however, few cases have been documented in recent years.3–6 In Japan, such reports are uncommon.7 Most patients have smouldering myeloma, and no precise treatment approach has been identified. Reports on patients receiving alkylating reagent treatment do not detail their responses, outcomes, and survival conditions. Herein, we report the case of a patient with symptomatic MM that occurred 15 years after receiving hydroxyurea (HU) for the treatment of PV, along with details of the clinical course, response, and outcomes of the two concomitant diseases after bortezomib-based treatment. Although the response and prognosis of MM, a fetal hematologic neoplasm, has improved with the recent introduction of new drugs,8 it is clinically important to observe the response and outcome of this rare type of MM, which occurs in the course of other hematologic neoplasms.

2 | CASE PRESENTATION

2.1 | Diagnosis and treatment of PV

An 81-year-old Japanese woman was referred to our hospital for the management of erythrocytosis 15 years prior to the diagnosis of MM. Laboratory data revealed a normal differential count of white blood cells (WBC), 17,010/μl; red blood cells (RBC), 800 × 10⁴/μl; hemoglobin (Hb), 20.6 g/dl; hematocrit (Hct), 60%; mean corpuscular volume (MCV), 83 fl; platelet count (PLT), 44.6 × 10⁴/μl; and a low serum erythropoietin level, 4.0 mU/ml. Bone marrow (BM) aspiration revealed hypercellular BM with a normal number of blast cells. Karyotype analyses of...
the BM revealed normal cells. Computed tomography revealed mild splenomegaly. The JAK2V617F mutation assayed in 2018 was positive. These findings met the diagnostic criteria for PV described by the World Health Organization.9 At the time of diagnosis, serum electrophoresis and urine protein test results were negative for monoclonal proteins. BM analysis revealed that plasma cells accounted for 0.4% of BM cells, with no abnormal plasma cell growth. The patient was administered HU 500 mg/day or every other day along with therapeutic phlebotomies (300 ml each time). The Hb and Hct levels were maintained at <15 g/dl and 45%, respectively. The patient’s symptoms were controlled with no underlying issues for approximately 15 years until the onset of acute renal dysfunction (Figure 1). A total of 1689 g of HU was administered before the diagnosis of MM.

2.2 | Diagnosis and treatment of MM

The patient presented at our hospital with anorexia and general fatigue. The complete blood count test results were as follows: WBC, 24,670/µl (myelocyte, 0.5%; bands, 2.5%; segmentation, 78%; monocytes, 3%; eosinophils, 4%; basophils, 1.5%; and lymphocytes, 9.5%); RBC, 468x10⁶/µl; Hb, 12.7 g/dl; Hct, 39.8%; MCV, 85 fl; and PLT, 50.7x10⁹/µl. Blood chemistry test results revealed elevated blood urea nitrogen, serum creatinine, and β2-microglobulin levels of 89 mg/dl, 12.5 mg/dl, and 44.7 mg/dl, respectively, indicating significant renal function impairment. Approximately 3 weeks before this episode, the patient had visited a different clinic with complaints of severe diarrhea and fever. Antidiarrheal and antifebrile drugs were prescribed, but her symptoms persisted for 10 days. Laboratory examination also revealed λ-type Bence Jones protein (BJP) in her serum and urine. Dehydration resulting from diarrhea and fever, along with the presence of BJP, potentially contributed to renal dysfunction and damage. The serum Ig levels were as follows: IgG, 432 mg/dl; IgA, 13 mg/dl; IgM, 36 mg/dl; free serum κ light chain, 19 mg/L; free serum λ light chain, 8150 mg/L; and κ/λ ratio, 0.002. BM examination revealed abnormal growth of atypical plasma cells (23.6% of BM cells) (Figure 2A). BM plasma cells were confirmed via staining with anti-CD38, and staining with anti-κ and λ light chains revealed λ-light chain restriction (Figure 2B,C). The karyotyping of the BM cells yielded normal results, and fluorescence in situ hybridization was negative for t(4;14). Although bone damage, hypercalcemia, and anemia were not observed, severe renal dysfunction led to the diagnosis of symptomatic MM.10 HU administration was discontinued upon the diagnosis of renal failure. The patient was immediately referred to the nephrology department for hemodialysis. Hemodialysis therapy (three times weekly for 2 weeks) resulted in gradual recovery of renal function. She was then treated with a bortezomib/cyclophosphamide/dexamethasone (BCD) regimen as described by Yagi et al.11 Each cycle consisted of a fixed dose of subcutaneous bortezomib (1.3 mg/m² weekly for 3 weeks), oral cyclophosphamide (50 mg daily for 21 days), and oral dexamethasone (20 mg weekly for 3 weeks). BM examination after four cycles of BCD revealed a 0.4% reduction in BM plasma cells and an absence of BJP in

FIGURE 1 Clinical course of polycythemia vera (PV). The patient was diagnosed with PV 15 years prior and was well maintained with hydroxyurea and therapeutic phlebotomy until the acute onset of renal dysfunction. The patient was diagnosed with MM. MM, multiple myeloma; PLT, platelet
FIGURE 2  (A) Bone marrow smear exhibiting abnormal growth of atypical plasma cells (23.6% of bone marrow cells) by May–Giemsa staining (x1000). (B) Confirmation of the nature of the plasma cells upon positive staining with anti-CD38 antibodies (x400). (C) Plasma cells showing λ-light chain restriction upon staining with anti-κ/λ light chain antibodies (x200). Left: anti-κ light chains; right: anti-λ light chains.

FIGURE 3  Hemodialysis and subsequent treatments for managing multiple myeloma. Renal function recovered after hemodialysis therapy followed by BCD treatment. After four cycles of BCD, the patient achieved and maintained stringent complete remission through two more cycles of BCD. Maintenance therapy with pomalidomide and dexamethasone was continued. κ, λ: serum-free light chains (mg/L); BJP: Bence Jones protein; BCD: bortezomib/cyclophosphamide/dexamethasone; BM: bone marrow; BUN: blood urea nitrogen (mg/dl); creatinine (mg/dl); Hb: (g/dl); WBC: /μl; PLT: x10⁴/μl.
the urine (Figure 3). The $\kappa/\lambda$ ratio had normalized, and immunohistochemical examination of the BM revealed no abnormal plasma cell proliferation (data not shown). The disappearance of BJP and $\kappa/\lambda$ ratio normalization was confirmed twice. The patient achieved stringent complete remission (sCR) based on the International Myeloma Working Group criteria. The only adverse effect observed was grade II stomatitis. Serum creatinine levels gradually recovered during treatment. Maintenance therapy with pomalidomide (2 mg daily for 21 days) and dexamethasone (20 mg weekly for 28 days) was administered after six cycles of BCD.

3 | OUTCOME AND FOLLOW-UP

At the time of writing this report, the patient was in sCR after receiving nine cycles of maintenance therapy. PV was observed without specific therapy during the course of BCD and maintenance therapy, although the results of the JAK2 mutation assay after six cycles of BCD remained positive.

4 | DISCUSSION

The coexistence of MM and PV is rare, and the treatment of MM under these conditions has not been described in detail. MM was previously considered an incurable hematologic neoplasm, with patients rarely achieving complete remission with alkylating reagents and steroids. The introduction of new drugs, such as bortezomib (protease inhibitor), lenalidomide, pomalidomide, and several other novel drugs, has significantly improved treatment and prognosis. Complete remission has been observed in some patients treated with these novel drugs, thereby providing a chance for a cure. To our knowledge, this is the first case report that details the clinical course, response, and outcome of symptomatic MM associated with PV treated with new drugs. Bortezomib was originally administered twice a week; however, considering the patient’s age, the drug was better tolerated when administered once a week, which is reportedly associated with fewer adverse effects, particularly in elderly Japanese patients. Our patient responded well to BCD therapy and achieved sCR. Ishida et al.15 previously demonstrated the efficacy of lenalidomide as maintenance therapy after remission induction by a bortezomib regimen in elderly Japanese patients. As lenalidomide is not ideal for patients with renal dysfunction, pomalidomide was used in our patient. Following the treatment for MM, PV was confirmed to still be JAK2 mutation-positive but was clinically stable without specific chemotherapy to PV at the present time. The favorable outcome in this case encourages the modification of treatment options for MM associated with other hematologic neoplasms.

In the present case, MM was diagnosed 15 years after PV, whereas, in previous reports, signs of both diseases were observed at the time of diagnosis. Although the actual MM onset time in our case was unclear, it was unique in that MM was observed long after the PV diagnosis and treatment. The patient received continuous HU treatment before the diagnosis of MM. Some anti-cancer reagents and radioactive P32 have tumorigenic or leukemogenic effects, but HU is reportedly the least tumorigenic agent for treating myeloproliferative neoplasia (MPN), including PV. We speculate that HU did not cause MM despite the exact etiology being unclear.

MPN including PV have also been associated with monoclonal gammopathy. Randi et al.18 and Javorniczky et al.20 reported monoclonal gammopathy in 8.2% out of 61 patients with MPNs. Randi et al.18 and Javorniczky et al.20 reported these rates to be 3.1% and 9% of cases, respectively, identifying higher rates in such patients than those in age- and sex-matched controls; however, these results were not statistically significant. Whether such a coexistence is coincidental or whether the two diseases share a common oncogenic factor remains unclear.

PV is a clonal disorder of stem cells, whereas MM is a clonal disorder of hematopoietic or lymphoid stem cells that involves terminally differentiated B cells. However, the clonality of these two concomitant diseases remains unclear. The involvement of B-lymphoid cells in PV has been demonstrated in patients who are heterozygous at the G-6PD locus. Recently, MM and MPN clones were directly analyzed in patients with JAK2 mutations, a characteristic acquired mutation found in patients with MPN, Lee et al.22 demonstrated JAK2 mutations in both myeloid and CD138-sorted plasma cells of two patients with smoldering MM associated with JAK2 mutation-positive PV, suggesting shared stem cell progenitors of MM and PV. Conversely, Kuroda et al.23 reported that the plasma cell fraction was negative for JAK2 mutations in a patient with MM associated with JAK2-positive essential thrombocytopenia, another type of MPN, suggesting different origins in their patient. Thus, MM and MPN clones may differ across cases. Our patient was positive for the JAK2 mutation, but we were unable to verify the presence or absence of this mutation in sorted plasma cells because hemodialysis and MM treatment were urgently required. The inclusion and analyses of additional cases are required to better elucidate the frequency, mechanisms,
clonal origin, optimal treatment, and prognosis of coexisting diseases.

AUTHOR CONTRIBUTIONS
HK was responsible for drafting and coordinating the final manuscript. HK, MF, HM, YS, and TK were involved in managing the patient. JA and KS are involved in renal failure management. All the authors have reviewed the manuscript.

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Materials from other sources were not included in this article.

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