Case Report

An Unprecedented Case of p190 BCR-ABL Chronic Myeloid Leukemia Diagnosed during Treatment for Multiple Myeloma: A Case Report and Review of the Literature

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We report the case of a 76-year-old man who was diagnosed as having chronic myeloid leukemia (CML) with p190 BCR-ABL while receiving treatment for symptomatic multiple myeloma (MM). The diagnosis of MM was based on the presence of serum M-protein, abnormal plasma cells in the bone marrow, and lytic bone lesions. The patient achieved a partial response to lenalidomide and dexamethasone treatment. However, 2 years after the diagnosis of MM, the patient developed leukocytosis with granulocytosis, anemia, and thrombocytopenia. Bone marrow examination revealed Philadelphia chromosomes and chimeric p190 BCR-ABL mRNA. Fluorescence in situ hybridization also revealed BCR-ABL-positive neutrophils in the peripheral blood, which suggested the emergence of CML with p190 BCR-ABL. We report here a case of coexisting MM and CML with p190 BCR-ABL. Given the rarity of this case, we also discuss the origins of these hematologic malignancies and review the relevant literature.

1. Introduction

Multiple myeloma (MM) is a lymphoid cancer that is characterized by monoclonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the serum, and organ dysfunction [1]. Chronic myeloid leukemia (CML) is a clonal disorder of myeloid origin that is characterized by the Philadelphia chromosome, t(9; 22) (q34; q11), in which the BCR-ABL fusion gene is created. Several types of BCR-ABL are known, with the p210 and p190 types being the most common, distinguished by the breakpoint in the BCR gene. The vast majority of CML cases result from the p210-type of BCR-ABL, while the p190-type is rarely found in CML [2]. The coexistence of MM and CML in the same patient is rare, with only 22 reported cases [3–23], all involving p210 BCR-ABL. Therefore, we report a case of coexisting MM and CML with p190 BCR-ABL. Given the rarity of this case, we also discuss the origins of these hematologic malignancies and review the relevant literature.

2. Case Report

A 76-year-old man was referred to our hospital in September 201X, because of right leg pain, lower back pain, and weight loss of 3 kg. Lumbar magnetic resonance imaging and computed tomography (CT) suggested the presence of lumbar spinal canal stenosis and a sacral tumor (Figure 1(a)). Laboratory testing revealed a markedly elevated serum IgG level (5,436 mg/dL, normal: 800–1,800 mg/dL) and an elevated serum beta-2 microglobulin level (4.1 µg/mL, normal: 0–3 µg/mL), although there were...
no signs of anemia, renal dysfunction, or proteinuria. Serum immunofixation revealed IgGκ-type M-protein, with an estimated serum-free κ and λ chain ratio of 21.5:1 (Figure 1(b)). Microscopic examination and flow cytometric analysis of bone marrow aspirate revealed elevated numbers of CD138-positive abnormal plasma cells. Cytogenetic analysis of the bone marrow revealed 46XY, and the patient was diagnosed as having MM (R-ISS, stage II). Chimeric p190 BCR-ABL mRNA was not detected in the bone marrow sample at this point. The patient underwent two cycles of bortezomib plus dexamethasone and two cycles of cyclophosphamide, bortezomib, and dexamethasone (CBD) but did not respond to either treatment regimen. The treatment was switched to lenalidomide (25 mg/day) plus dexamethasone (20 mg/week; Ld therapy), and there was a marked response, with a substantial decrease in the M-protein and disappearance of the sacral tumor on CT. After 24 cycles of Ld therapy, the patient achieved a partial response based on the International Myeloma Working Group criteria.

In December 201X+2, the patient developed leukocytosis (white blood cell count: 35.8 × 10^9/L) and thrombocytopenia.
## Table 1: Concomitant multiple myeloma and chronic myeloid leukemia cases.

| Pt | Age/Sex | Year | First disease | Diagnosis interval (month) | Type of M-protein | Therapy for MM | Therapy for CML | Confirmation method of Ph+ | Type of Ph | Reference |
|----|---------|------|---------------|-----------------------------|-------------------|----------------|----------------|---------------------------|------------|-----------|
| 1  | 77M     | 1972 | MM           | 33                          | BJP               | No treatment  | No treatment | Chr                        |            | MacSween and Langley [3] |
| 2  | 65/F    | 1974 | CML          | 113                         | IgG-κ             | No treatment  | Busulfan      | Chr                        |            | Derghazarian and Whittemore [4] |
| 3  | 58/M    | 1982 | Simultaneous | 24                          | IgG-κ             | MP, RT        | HU, Busulfan, | Chr                        |            | Boots and Pegrum [5] |
| 4  | 71/M    | 1993 | Simultaneous | 33                          | IgG-κ             | Not reported  | No treatment | Chr                        |            | Klenn et al. [6] |
| 5  | 72/F    | 1998 | Simultaneous | 24                          | IgG-κ             | VP            | IFN-α         | Chr, PCR, FISH              | P210       | Tanaka et al. [7] |
| 6  | 70/M    | 1999 | MM and CML   | 33                          | IgG-κ             | Not reported  | Not reported  | Chr                        |            | Nitta et al. [8] |
| 7  | 81/M    | 2001 | Simultaneous | 113                         | IgA-κ             | MP            | No treatment | Chr, PCR                   | P210       | Alvarez-Larrán et al. [9] |
| 8  | 66/M    | 2003 | Simultaneous | 33                          | IgG-κ             | MP            | INF-α, HU, Busulfan | Chr, PCR, FISH | P210       | Schwarzmeier et al. [10] |
| 9  | 47/M    | 2003 | MM           | 33                          | BJP               | LOAD-IN       | Not reported  | IFN-α, imatinib             | Chr, PCR | P210       | Gallipoli et al. [12] |
| 10 | 68/M    | 2005 | CML          | 20                          | IgG-λ             | MP            | Not reported  | Chr                        |            | Romanenko et al. [13] |
| 11 | 85/F    | 2005 | MM and CML   | 33                          | IgG-λ             | Not reported  | Not reported  | Chr, PCR                   | P210       | Alsidawi et al. [14] |
| 12 | 76/M    | 2009 | CML          | 14                          | IgA-κ             | MP            | IFN-α, imatinib | Chr, PCR, FISH | P210       | Michael et al. [15] |
| 13 | 57/F    | 2009 | CML          | 65                          | IgA-κ             | TD, VAD       | Imatinib      | Chr                        |            | Ide et al. [16] |
| 14 | 72/F    | 2010 | MM and CML   | 65                          | IgG-κ             | No treatment  | Imatinib      | Chr                        |            | Offiah et al. [17] |
| 15 | 71/F    | 2012 | Simultaneous | 33                          | IgG-κ             | MP, Bd, Ld    | Imatinib      | Chr                        |            | Romanenko et al. [18] |
| 16 | 64/F    | 2013 | Simultaneous | 17                          | IgG-κ             | RT, VCD, VCDD, VRD | Dasatinib | Chr, PCR                   | P210       | Ragupathi et al. [19] |
| 17 | 62/F    | 2013 | MM and CML   | 17                          | IgG-κ             | RT, BD        | No treatment  | Chr, PCR                   | P210       | Maerki et al. [20] |
| 18 | 77/M    | 2014 | Simultaneous | 48                          | IgG-κ             | RT, Ld        | No treatment  | Chr, PCR                   | P210       | Alsidawi et al. [21] |
| 19 | 60/M    | 2014 | MM and CML   | 120                         | IgG-κ             | BD, Ld        | Imatinib      | Chr                        | P210       | Pessach et al. [22] |
| 20 | 63/F    | 2012 | MM and CML   | 54                          | IgG-λ             | VAD           | Imatinib      | Chr                        | P210       | Pessach et al. [22] |
| 21 | 76/M    | 2015 | MM and CML   | 38                          | IgA-λ             | No treatment  | Imatinib      | Chr                        | P210       | Ahn et al. [23] |
| 22 | 51/F    | 2016 | MM           | 38                          | Unknown           | IgG           | Imatinib      | Chr                        |            | Wolleschak and Heidel [24] |
| 23 | 88/M    | 2016 | Simultaneous | 28                          | IgG-κ             | LR            | Imatinib      | Chr                        |            | Ali et al. [25] |
| 24 | 76/M    | 2018 | MM and CML   | 28                          | IgG-κ             | Ld            | Dasatinib, bosutinib | Chr, PCR, FISH | P190      | Our case |

BJP, Bence Jones protein; MP, melphalan, prednisolone; RT, radiation therapy; HU, hydroxyurea; LOAD-IN, melphalan, ranimustine, vincristine, IFN-α; PSL, prednisolone; VCD, bortezomib, cyclophosphamide, dexamethasone; VCDD, VCD plus doxorubicin; VRD, bortezomib, lenalidomide, dexamethasone; LD, lenalidomide, dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; BD, bortezomib, dexamethasone; CBD, BD plus cyclophosphamide; Rd, lenalidomide, dexamethasone; TD, thalidomide, dexamethasone; Chr, chromosome; PCR, polymerase chain reaction; FISH, fluorescence in situ hybridization.
(platelet count: $3 \times 10^9$/L). Bone marrow biopsy and aspiration revealed hypercellularity with a marked increase in myeloid lineage cells but without an increase in blast cells (4%). Cyogenetic analysis revealed 46XY t(9; 22) (q34; q11.2) in 20 of 20 cells, and fluorescence in situ hybridization (FISH) analysis revealed that 99.5% of the cells were positive for BCR-ABL. Peripheral blood neutrophils were also positive for BCR-ABL (98.8%) (Figures 2(a)–2(b)). Chimeric p190, but not p210, BCR-ABL mRNA was detected by using polymerase chain reaction (Figure 2(c)). The diagnosis was confirmed to be CML with p190 BCR-ABL in the accelerated phase (AP), which coexisted with MM (a maintained partial response). Dasatinib treatment (100 mg/day) was started immediately. The dose was subsequently decreased to 50 mg/day, due to the persistence of thrombocytopenia. In April 201X+3, a bone marrow examination indicated that the patient had achieved a second chronic phase, with 31% of this cells being positive for BCR-ABL upon FISH analysis, and that his peripheral blood count had normalized. However, 5 months later, FISH analysis revealed that 85.8% of his bone marrow cells were positive for BCR-ABL, and subsequently, his treatment was changed from dasatinib to bosutinib. This switch appeared to be ineffective, as no decrease in the BCR-ABL-positive bone marrow cells was detected after 2 months.

3. Discussion

There have only been 24 cases of coexisting MM and CML reported (Table 1) [3–25]. MM and CML were diagnosed simultaneously in 9 cases, and the diagnoses were sequential in the remaining cases, with MM being diagnosed first in 8 cases and CML being diagnosed first in 7 cases. Among the previous reports, all genotypes confirmed by PCR were p210-CML in patients with coexisting MM and CML. Our case is the first reported of MM coexisting with p190-CML in the same patient. The intervals between the sequential diagnoses ranged from 3 months to 120 months. Multiple possibilities could be considered regarding the association between MM and CML. First, these two malignancies could occur independently, and their coexistence, while very rare, could be simply coincidence. Second, common precursors, referred to as “clonal hematopoiesis of indeterminate potential (CHIP),” give rise to both MM and CML cells in a patient. Given our patient’s relatively advanced age, it is possible that CHIP had a common origin, although we have no direct evidence to support this possibility. A third possible explanation is that the second disease might be a therapy-related malignancy that develops after treatment for the first disease. In the present case, the diagnosis of MM was followed by that of CML. The frequency of secondary carcinogenesis in patients with MM was evaluated for cohorts participating in clinical trials with lenalidomide, which were conducted from 2000 through 2012 [24]. This report showed that the incidence of secondary hematologic malignancies was increased in patients who concurrently received melphalan and lenalidomide, while it did not increase in those receiving other treatment protocols, regardless of whether lenalidomide was included [26]. There is no clear evidence that lenalidomide is carcinogenic, and there has only been one reported case of CML that developed after lenalidomide treatment. Therefore, the increased incidence of hematologic malignancies has been attributed to melphalan, because alkylating agents such as melphalan are known to cause therapy-related myelodysplastic syndromes. According to previous case reports of MM coexisting with CML, many patients received alkylating agents as treatment for MM (Table 1). In the present case, a small dose of an alkylating agent (cyclophosphamide; total: 2,400 mg/m²) was administered during two cycles of CBD therapy. We, therefore, needed to consider the possibility that the cyclophosphamide treatment caused the CML. However, an accumulation of case reports and further investigations are required to draw definitive conclusions.

Although p190 BCR-ABL CML has been reported in 1% of CML cases, there have been several clinical observations suggesting that CML with p190 BCR-ABL is difficult to treat [27]. Furthermore, p190 BCR-ABL has been identified as a marker for high-risk disease, and early stem cell transplantation has been recommended if the patient is eligible [26]. Our patient received initial treatment of dasatinib for his CML in AP with p190 BCR-ABL, which provided a partial cytogenetic response at 4 months after the diagnosis. Although the long-term effects of dasatinib treatment in patients with p190 BCR-ABL CML are unknown, in the present case, the duration of response to dasatinib was relatively short.

Ethical Approval

This study was adhered to the tenets of the Declaration of Helsinki.

Consent

Informed consent was obtained from the patient.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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