Multiple myeloma in a patient with chronic myeloid leukemia: A case report

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Abstract. Chronic myeloid leukemia (CML), a clonal myeloproliferative disorder of pluripotent hematopoietic stem cells, results from the Philadelphia chromosome (Ph) chromosome. The Ph is from a translocation, t(9;22)(q34q11), that creates a BCR-ABL fusion gene, which is transcribed into proteins with abnormal tyrosine kinase activity, driving the abnormal proliferation of white blood cells. Multiple myeloma (MM) is a proliferation disorder of plasma cells derived from a single clone, which may lead to uncontrolled growth, kidney injury, destructive bone lesions, hypercalcemia and anemia. It is extremely rare that MM and CML should occur in the same patient either synchronously or metachronously. To date, MM accompanied with CML has only been reported in limited studies, and the the cause behind the occurrence of both malignancies together is not understood. With the advent of novel therapies, the survival time in patients with CML and MM has improved. Therefore, the further investigation of the pathophysiology and clinical characteristics of these cases is valuable. The present study reports the case of a 79-year-old male who had been diagnosed with CML and treated with tyrosine kinase inhibitor, and then developed immunoglobulin G-κ MM after 6 years. This report should provide valid raw data for clinical research.

Introduction

Chronic myeloid leukemia (CML) is a neoplasm of myeloid origin that has an annual incidence of 1 to 2 cases per 100,000 individuals worldwide and a mean age at time of diagnosis of 65 years (1,2). Multiple myeloma (MM) is a hematological malignancy that has characteristic abnormal clonal plasma cells present in the bone marrow. MM is diagnosed in an estimated 588,161 individuals worldwide each year and a median age at time of diagnosis of 70 years (3,4). To the best of our knowledge, these 2 uncommon diseases in the same patient is extremely rare, and, since 1972, there have been 15 cases reported in the world literature. MM accompanied by CML is rare, and few related studies have been reported worldwide since 1972 (5-8). A literature review shows that new hematopathological neoplasms occur following the initial treatment of a hematological malignancy (7,9-11). This can include a single or up to three new additional neoplasms subsequent to treatment. An example of this is the occurrence of MM following treatment of CML with tyrosine kinase inhibitor (TKI) (7). The origin of these two malignancies in such patients remains unknown, and further research is required to enhance our understanding. The present study describes the unusual case of a patient treated with TKI who developed MM 6 years after the diagnosis of CML.

Case report

A 79-year-old male was admitted to The First Affiliated Hospital of Jishou University (Jishou, China) in February 2016 due to a 2-month history of an unexplained fever combined with a cough and expectoration. Prior to hospitalization, the patient experienced an intermittent mild fever (~38.0˚C), mainly in the afternoon. Intravenous cephalosporin antibiotics (2 g ceftazidim twice a day for 3 days; 0.5 g moxifloxacin sodium chloride every day for 1 week) and fluid replacement were used to control the fever, but the efficacy was limited. The patient developed an oral ulcer during this time, but the symptoms improved after the aforementioned intravenous anti-inflammatory treatment. An initial hematological examination showed an elevated white blood cell (WBC) count of 43.86×10^9/l (normal range, 4.0-10.0x10^9/l) and a neutrophil count of 36.47×10^9/l (normal range, 1.8-6.3x10^9/l). Bone marrow aspiration revealed 85% granulocytes, mainly with hyperplasia of the mesocytic granulocyte and rod-shaped nuclear granulocytes (Fig. 1). Karyotype analysis detected Ph [t(9;22)(q34;q11)] in 8 out of 20 metaphases analyzed (Fig. 2). BCR-ABL t(9;22) translocation was also confirmed by fluorescence *in situ* hybridization (FISH) assays (Data S1), which showed fusion signals for [BCR-ABL1

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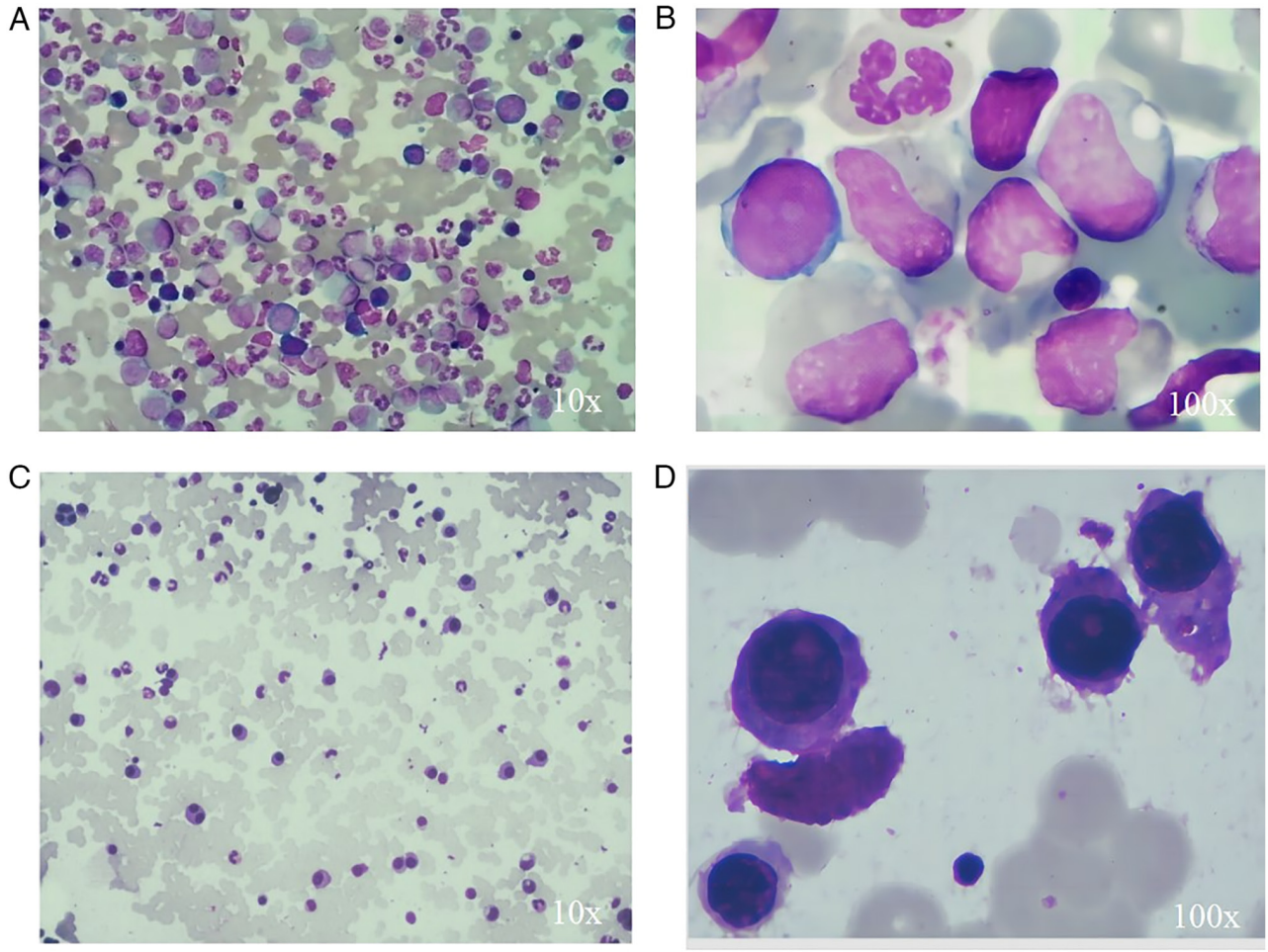

Figure 1. At the time of the chronic myeloid leukemia diagnosis, the bone marrow showed hypercellularity with marked myeloid hyperplasia. (A) x10 magnification; (B) x100 magnification. At the time of the multiple myeloma diagnosis, the bone marrow showed normal cellularity with plasma cells constituting 21% of the cells. (C) x10 magnification; (D) x100 magnification.

International Standard (IS), 71.833%]. A peripheral smear showed only rare blasts (<10%) and the patient appeared to be in the chronic phase of CML. The patient was diagnosed with CML (Sokal score 1.1) (12) in February 2016 and treated with imatinib (400 mg daily), with intermittent follow-up in the Outpatient Department. During this period, the patient was advised to change to a second-generation TKI owing to the poor efficacy of the initial treatment, but this was refused due to economic factors. In addition, due to these economic factors and the poor compliance of the patient, no patient-related data was obtained between February 2016 and September 2020, which is a deficiency of this case report. However, from the clinical data of the patient at the initial diagnosis of CML, there was no basis for active MM. The curative effect in the patient was still not satisfactory after treatment with imatinib for ~4 years [BCR-ABL1(IS), 33.902%]. Thus, the treatment was switched to flumatinib (600 mg daily) in September 2020. With regular follow-up, the BCR-ABL1(IS) count had decreased to 3.062% after 6 months (Fig. 3).

In April 2022, the patient complained of bone pain and was found to exhibit a high level of immunoglobulin (IgG) (30.40 g/l; normal range, 7.51-15.60 g/l). Further work-up revealed IgG-κ monoclonality, with an M-spike of 39.82 g/l. Moreover, a skeletal survey revealed multiple bony lesions in the skull, but magnetic resonance imaging of the spine showed no obvious damage to the sclerotin. The β-2 microglobulin level reached 5.52 mg/l (normal range, 1.0-3.0 mg/l), and the serum calcium and renal function were normal. The serum κ free light chain level was elevated at 131.97 mg/l, with an increase in the κ:λ chain ratio at 13.8. A bone marrow smear showed 21% primitive plasma cells, and flow cytometry further demonstrated plasma cells positive for κ chain, CD38 and CD138 (Fig. 4). Flow cytometry was performed on a DxFLEX flow cytometer (Beckman Coulter, Inc.). Cytogenetic analysis of bone marrow cells revealed a normal male karyotype of 46, while the XY-FISH analysis (Fig. 5) detected a complex chromosome rearrangement [52,XY,+3,add(4)(q31),+7,add(7)(q32), +8,+11,-13,+15,+19,+mar[4]/46,XY[16]]. Therefore, the patient was diagnosed with IgG-κ MM, Durie-Salmon stage IIIA (13), International Staging System (ISS) stage III (14) and revised ISS stage II (15), and treated with combination chemotherapy using an VRd regimen [2 mg bortezomib on days 1, 4, 8 and 11; 25 mg lenalidomide on days 1-14; and 20 mg dexamethasone (DXM) on days 1 and 2, 4 and 5, 8 and 9, and 11 and 12; 28-day cycles]. After two cycles of chemotherapy, the curative effect did not reach a partial response status, so the scheme was adjusted to a DVD regimen (800 mg daratumumab on days 0, 7, 14 and 21; 2 mg bortezomib on days 1, 4, 8 and 11;

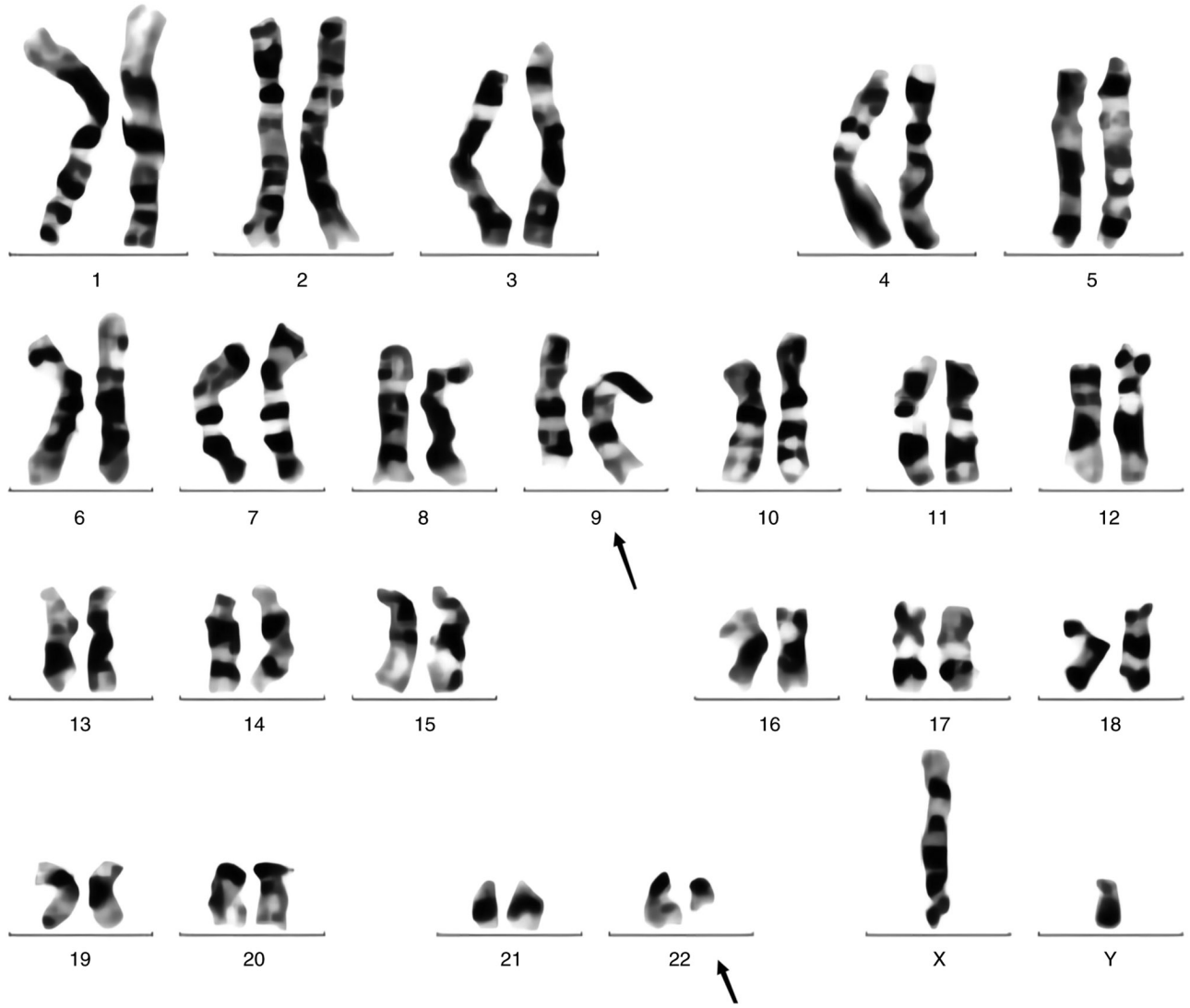

Figure 2. Karyotype from a bone marrow specimen at the time of the chronic myeloid leukemia diagnosis. The translocation t(9;22) is shown using arrows.

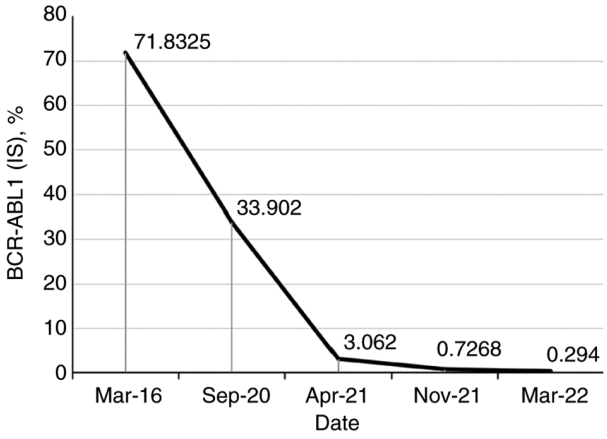

Figure 3. Changing trend in BCR-ABL1(IS) level. IS, International Standard.

and 20 mg DXM on days 1 and 2, 4 and 5, 8 and 9, and 11 and 12; 28-day cycles). After one cycle, the monoclonal Ig level decreased markedly to 11.97 g/l (Fig. 6). The patient continued to receive 600 mg flumatinib when at home, and the general condition of the patient was reported to be good, although no further laboratory results were obtained.

Discussion

CML is a myeloproliferative disorder caused by pluripotent hematopoietic stem cells. MM is a monoclonal disorder of plasma cells that have differentiated from lymphoid B cells. The abnormal cell types of CML and MM are therefore distinctly different. The mechanism of these two concomitant malignant tumors is not fully understood. Several factors have been postulated to be related to the presence of accompanying diseases, including host-specific characteristics, prior chemotherapy and radiation, exposure to environmental carcinogens or radiation, and epigenetic upregulation/downregulation. The present study discusses some assumptions about the mechanism of MM accompanying CML.

First, an intuitive hypothesis is that MM arises as a consequence of the therapy for CML (16). Several studies reviewed the association between chemotherapy and the development of MM in the months following treatment, particularly in imatinib-treated CML (7,17). During the treatment of CML,

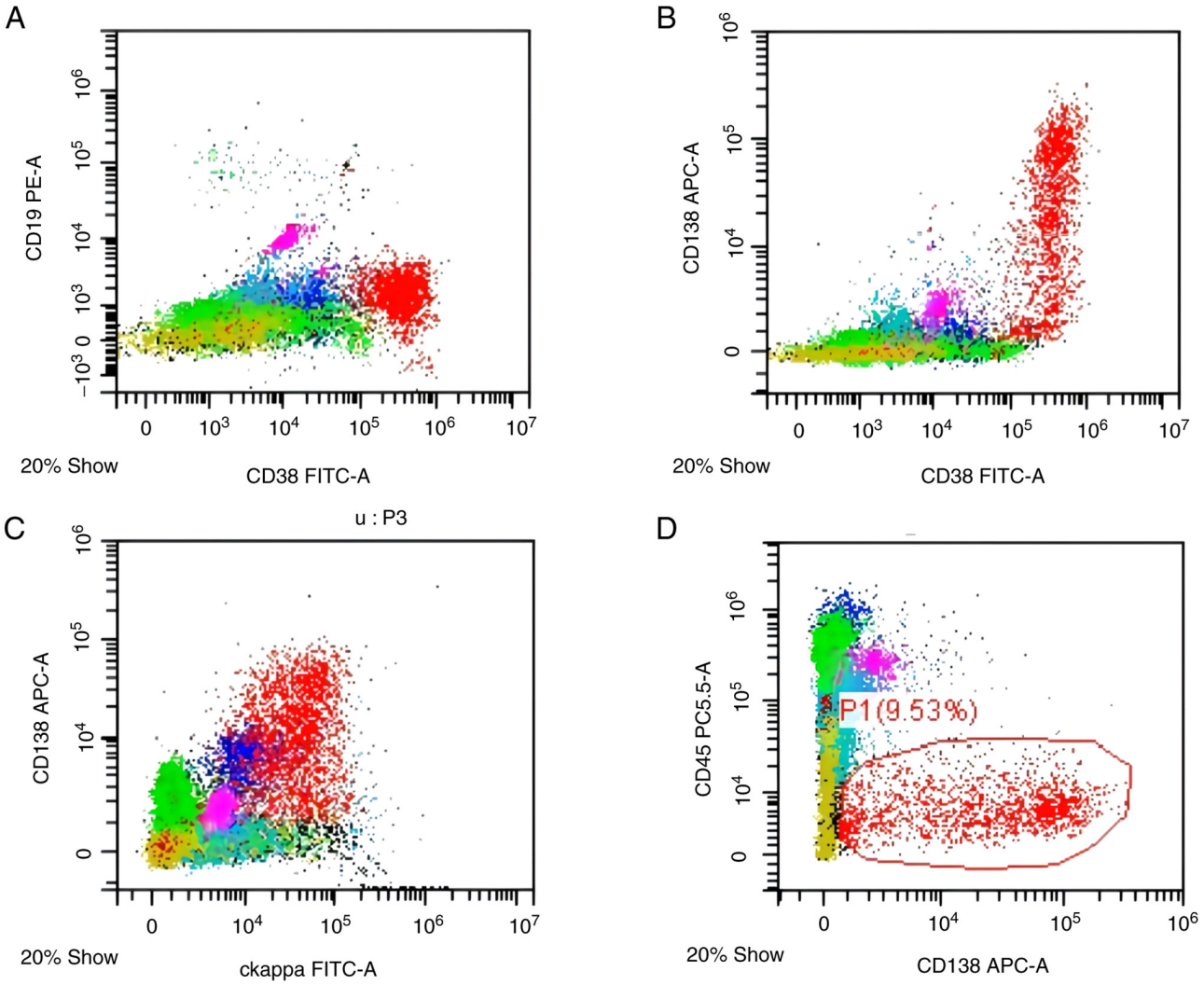

Figure 4. Flow cytometry analysis of bone marrow cells. Plasma cells were positive for CD38, CD138 and immunoglobulin κ light chain restriction expression. (A Expression of CD38, but not CD19. (B) Expression of CD38 and CD138. (C) CD138 and cKappa were expressed. (D) Expression of CD138, but not CD45.

imatinib inhibits the proliferation of WBCs by competing with ATP to bind to BCR-ABL1 tyrosine kinase. In addition, imatinib mesylate is active in different genes involved in cell transformation, and can inhibit BCR-ABL1, c-KIT, PGFRα/β, Jak2 and Erk1/2 (5). In a study from 2010, the use of imatinib mesylate in the treatment of CML was shown to increase the risk of MM. It was suggested that all patients treated with imatinib should be regularly monitored by serum protein electrophoresis (18). This study provided support for the plasmacyte-specific effects of imatinib. By contrast, another study revealed that imatinib inhibits the proliferation of MM cells by arresting cell cycle progression (19). As a result, no conclusion can be made at this point due to the conflicting results of published studies. The long-term effects of TKIs must continue to be closely monitored due to the lack experience in their use and the few cases reported.

Another potential hypothesis is that plasma cell myeloma and CML share the presence of malignant pluripotent progenitor stem cells (16,20,21). This reveals the capability of CML to differentiate into either myeloid lineage or lymphoid lineage. A previous study analyzed whether overlapping genetic susceptibility loci were present in myeloproliferative neoplasm (MPN) and MM (21); 23 known MM risk sites were assessed in individuals from MPN case-control studies, and the most significant result was noted for PS0RS1C1-rs2285803 in patients with CML. The polygenic risk score showed that PS0RS1C1-rs2285803 is related to CML risk, suggesting that the combination of multiple MM risk loci may affect CML risk, and vice versa. This implies a potential common genetic background between CML and MM (21), which requires further investigation. Meanwhile, the constitutively active BCR-ABL tyrosine kinase is known to promote cell survival and proliferation, and is responsible for the malignant transformation of the disease (11). Furthermore, Ph has been associated with an increase in cell proliferation and survival, as well as malignant transformation, and has been detected in all hematopoietic cell lineages (16,21-23). Although the etiology of CML and MM in the present patient could not be determined, the hypothesis that the diseases evolved from common malignant pluripotent hematopoietic stem cells has potential.

Thirdly, the presence of host-specific factors is also an explanation for the dual presence of the diseases in the same patient; preexisting CML may create a more sustainable environment for the formation of secondary malignancies. Plasma cell myeloma (PCL) is a slow growing malignancy that

Figure 5. Karyotype from a bone marrow specimen at the time of the multiple myeloma diagnosis showing 52,XY,+3,add(4)(q31),+7,add(7)(q32),+8,+11,-13,+15,+19,+mar[4]/46,XY[16].

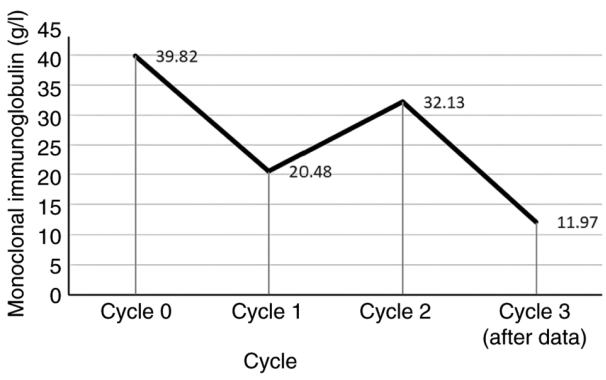

Figure 6. Quantification of monoclonal immunoglobin in the course of treatment. Dara, daratumumab.

develops over a number of years. This in return may reduce the effectiveness of the immune system, thus impeding its ability to destroy newly formed malignant cells. The patients may present with seemingly simultaneous malignant tumors. Notably, given the large number of chromosomal abnormalities existing in the present patient, the genetic instability of the host may have produced an atypical progenitor cell, placing this patient in a more vulnerable position to acquire multiple disorders. Furthermore, during the treatment, the expression of NF-κB signaling pathway is downregulated, and these malignant cells gain anti-apoptotic abilities and mechanisms, and evade immune surveillance in the context of immune response loss or decline (5,6,23,24). The progression or treatment of malignant tumors enhances the development of malignant cells (gaining anti-apoptotic abilities) and the mechanisms of evading immune surveillance, chronic antigen stimulation and genetic polymorphism (23,25). In addition, the variability of enzymes and repair pathways encoded by genes may make a person more likely to develop malignant tumors (5). These properties of MM suggest that these changes to the microenvironment of the bone marrow may create sustainability and opportunity for secondary hematopathological malignancies.

In conclusion, MM in a patient with CML is extremely rare. The reasons for the occurrence of both diseases in one patient may be multifactorial, so the exact mechanism of the

present extremely rare case remains unknown. Therefore, further investigation and monitoring of potential associated cases is needed to determine the exact cause of concomitant multiple malignant tumors.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

XLL and KS conceived and designed the study. XLL collected all relevant data of patients from the database and drafted the manuscript, while MLi was responsible for medication guidance. ZWS and LZW analyzed the data. KS revised the manuscript. KS, JT and MLia participated in making the pathological diagnosis. All authors confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The First Affiliated Hospital of Jishou University.

Patient consent for publication

Written consent for publication of the case report and any accompanying images, without any potentially identifying information, was provided by the patient's family.

Competing interests

The authors declare that they have no competing interests.

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