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Letter

Coexistence of myeloproliferative neoplasms with multiple myeloma☆

Qiuqing Xiang, Bin Chu, Minqiu Lu, Lei Shi, Yutong Wang, Lijuan Fang, Yuan Chen, Kai Sun, Li Bao *

Department of Hematology, Beijing Jishuitan (JST) Hospital, Capital Medical University, Beijing 100096, China

Managing Editor: Peng Lyu
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Myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis, originate from pluripotent hematopoietic stem cells and are characterized by the clonal proliferation of one or more peripheral blood lineages, often accompanied by hepatosplenomegaly, thrombosis, and extramedullary hematopoiesis.[1] Multiple myeloma (MM) is a plasma cell (PC) malignancy of terminally differentiated B lymphocytes.[2] The co-occurrence of MM and MPN is rare. There are a few reports of ET co-occurring with MM,[3–5] with MM manifesting simultaneously with or several years after ET. PV combined with MM is much rarer; in most cases, MM manifests a few years after PV, and only nine cases of PV occurring simultaneously with MM have been reported.[6] There is no standard treatment protocol for MM combined with MPN. Here, we report two cases of MPN co-occurring with MM after several years of hydroxyurea treatment to provide a clinical reference.

The first patient was a 76-year-old woman with a 5-year history of hypertension. In November 2018, the patient presented to our hematology department with weight loss. Blood tests revealed a white blood cell (WBC) count of 54.3 × 10^9/L, a hemoglobin (Hb) concentration of 160 g/L, and a platelet (PLT) count of 1107 × 10^9/L. Bone marrow (BM) examination revealed grade I-II hyperplasia with active hyperplasia of all lineages, high PLTs, and marked hyperplasia of the megakaryocytes. Genetic testing revealed *JAK2V617F* mutation, but no mutations in *BCR-ABL1*, *MPL*, and *CALR*. An abdominal ultrasound revealed splenomegaly. The patient met the diagnostic criteria for *JAK2*-positive ET: (1) PLT 1107 × 10^9/L; (2) BM examination showing hyperplasia, high PLTs, and marked megakaryocyte hyperplasia; (3) the World Health Organization (WHO) diagnostic criteria for *BCR-ABL*-negative chronic myeloid leukemia, PV, primary myelofibrosis, myelodysplastic syndromes, or other myeloid tumors are not met; and (4) presence of *JAK2V617F* mutation. Therefore, the patient was diagnosed as having ET. The treatment regimen comprised hydroxyurea 1 g orally once a day, followed by regular outpatient monitoring of blood counts. Leukocytes and hemoglobin returned to normal ranges, and platelets fluctuated at 253–589 × 10^9/L. In April 2023, the patient had fatigue and weight loss, and a physical examination revealed clinical signs of anemia, including pallor of the skin and mucous membranes. Blood tests revealed a WBC of 1.17 × 10^9/L, Hb of 76 g/L, and PLT of 235 × 10^9/L. The patient stopped taking hydroxyurea immediately. After 1 week, blood tests revealed WBC, 0.73 × 10^9/L; Hb, 42 g/L; and PLT, 160 × 10^9/L. The patient was subsequently hospitalized. Biochemistry tests revealed total protein, 61.7 g/L; albumin, 43.8 g/L; calcium, 2.2 mmol/L; creatinine, 54 μmol/L; lactate dehydrogenase (LDH), 263 IU/L; beta-2 microglobulin, 2.29 mg/L; and an elevated total immunoglobulin A (IgA) level (1.95 g/L) with reciprocally decreased immunoglobulin G (IgG) and immunoglobulin M (IgM) levels. Serum and urine immunofixation electrophoresis revealed IgA-λ clonality. A skeletal survey showed osteopenia and a T12 vertebral compression fracture. No clonal PCs were detected in the peripheral blood by flow cytometric analysis. *JAK2V617F* mutation was detected in the peripheral blood, whereas *MPL* and *CALR* mutations were not detected. BM examination showed infiltration by PCs, which comprised up to 22 % of nucleated cells [Figure 1A]. The PCs were lambda-restricted and had cytoplasmic $CD138^+$ $CD38^+$ $CD27^+$ $CD269^+$ expression [Figure 1 B]. Fluorescence *in situ* hybridization was positive for t(11; 14), but no high-risk abnormalities, such as del(17p) or t(4; 14) and/or t(14; 16), were found [Figure 1C]. A BM biopsy revealed that BM proliferation was markedly reduced, with scattered PCs. Next-generation sequencing revealed mutations in *JAK2V617F*, *VCAN*, *KIT*, and *CCND1*. The patient was diagnosed with IgA-λ MM, Durie Salmon stage IIIA, International Staging System (ISS) stage I, and Revised ISS (RISS) stage I. She subsequently received a daratumumab, lenalidomide, and dexamethasone (DRd) chemotherapy regimen (daratumumab, 16 mg/kg on days 1, 8, 15, and 22; lenalidomide, 25 mg on days 1–14; dexamethasone,

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* Corresponding author: Department of Hematology, Beijing Jishuitan (JST) Hospital, Capital Medical University, Beijing 100096, China.
E-mail address: baoli@jst-hosp.com.cn (L. Bao).

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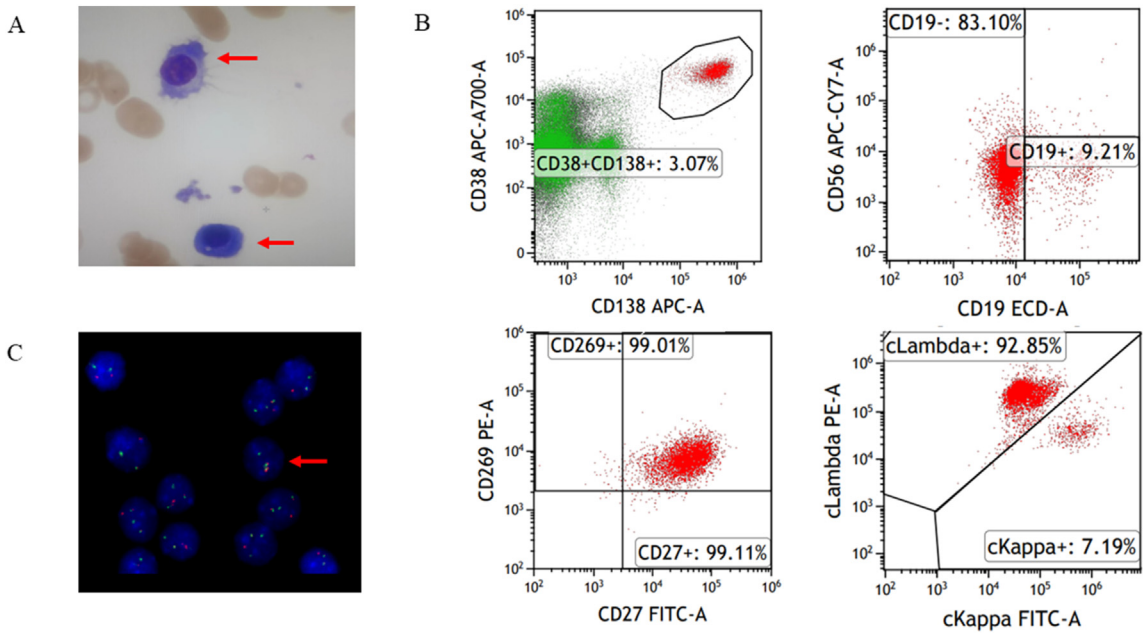

Figure 1. Bone marrow laboratory test results. (A) Bone marrow examination revealed infiltration by plasma cells (May-Giemsa, × 100); (B) The plasma cells were lambda-restricted and had cytoplasmic $CD138^+$ $CD38^+$ $CD27^+$ $CD269^+$ expression; (C) Fluorescence *in situ* hybridization was positive for t(11; 14).

20 mg on days 1, 8, 15, and 22 and subsequently, every 4 weeks). After 1 month, blood tests revealed WBC, 6.6 × 10^9/L; Hb, 98 g/L; and PLT 397 × 10^9/L. Subsequently, the patient refused to continue daratumumab, and we decided to keep her on oral lenalidomide combined with aspirin therapy. After 2 months, her PLT increased to 1132 × 10^9/L. The patient's peripheral blood showed manifestation of ET again, indicating the coexistence of the two diseases in the patient.

The second patient was a 67-year-old woman with a 20-year history of hypertension. In 2010, the patient presented to the hematology department with facial redness. Blood tests revealed WBC, 4.5 × 10^9/L; Hb, 200 g/L; and PLT, 245 × 10^9/L. BM examination revealed hypercellularity. Genetic testing revealed *JAK2V617F* mutation, but no mutations in *BCR-ABL1*, *MPL*, or *CALR*. The patient was diagnosed with PV. The treatment regimen comprised hydroxyurea 0.5 g orally three times a day, followed by regular outpatient monitoring of blood counts. In September 2023, the patient felt low back pain, and blood tests revealed WBC, 10.5 × 10^9/L; Hb, 150 g/L; and PLT, 460 × 10^9/L. BM examination revealed infiltration by PCs, which comprised up to 8.5 % of nucleated cells. A BM sample was submitted for flow-cytometric testing, which revealed an abnormal plasma-cell population (1.06%) strongly expressing CD38, CD138, and cytoplasmic λ. A BM biopsy revealed clonal PC hyperplasia. Reticular fiber staining was negative. Immunohistochemistry revealed $CD138^+$ $lambda^+$ $kappa^-$ on the plasma cell surface. Genetic testing revealed that *JAK2V617F* mutation was positive, whereas *BCR-ABL1*, *MPL*, and *CALR* mutations were negative. Subsequently, the patient was hospitalized in our department. Blood and biochemistry tests revealed WBC, 11.3 × 10^9/L; Hb, 151 g/L; PLT, 501 × 10^9/L; total protein, 45 g/L; albumin, 38 g/L; calcium, 2.39 mmol/L; creatinine, 56 μmol/L; LDH, 248 IU/L; beta-2 microglobulin, 2.42 mg/L, and an elevated total IgA level (23 g/L) with reciprocally decreased IgG and IgM levels. Serum and urine immunofixation electrophoresis revealed IgA-λ clonality and positron emission tomography/computed tomography (PET/CT) revealed no destruction or lytic lesions. Magnetic resonance imaging (MRI) of the vertebrae revealed multiple focal lesions in the vertebral body. Accordingly, the patient was diagnosed with IgA-κ MM, Durie-Salmon stage IIIA, ISS stage I. She received a bortezomib, lenalidomide, and dexamethasone (VRd) chemotherapy regimen (bortezomib, 1.3 mg/m^2 on days 1, 8, and 15; lenalidomide, 25 mg on days 1–14; dexamethasone, 20 mg on days 1, 8, and 15 and subsequently, every 3 weeks). Meanwhile, the patient stopped taking hydroxyurea. She is currently in the first course of treatment.

MM is an abnormal proliferation of clonal PCs, and MPN originates from pluripotent hematopoietic stem cells. The two diseases have different origins and rarely co-occur. ET combined with MM was first reported by Zimelman in 1973,[3] and since then, three cases have been reported in China and more than 20 cases in other countries. In most cases, MM appeared several years after ET, and in the case reported by Niscola et al.,[4] the progression of ET to concomitant MM even took 37 years. However, these two diseases can occur simultaneously. We here report a case of a patient with concomitant MM after ET, which suggests that not only should myelosuppression due to the use of hydroxyurea be considered in patients with decreased blood counts after prolonged and stable ET, but prompt BM aspiration with attention to the differential diagnosis should be performed. The TEMPI syndrome should be considered in patients with longstanding and unexplained erythrocytosis along with elevated erythropoietin levels and monoclonal gammopathy. Although our patient had a history of transient erythrocytosis, she is currently anemic and has a persistent *JAK2* mutation, ruling out the TEMPI syndrome. The second patient developed MM 13 years after the diagnosis of PV. More than 20 cases of PV combined with MM have been reported, of which only nine cases involved concurrent PV with newly diagnosed MM.[6] This indicates that the two diseases can occur simultaneously, but in most cases, MM develops many years after MPN.

The reason for the co-occurrence of the two tumors is unknown, but there are several possible causes. First, pluripotent hematopoietic stem cells can differentiate into myeloid and lymphoid lineages, and both diseases may have a common origin.[7] Second, interleukin-6 (IL-6) is a potent human myeloma cell growth factor and an important component of MM pathogenesis and progression.[8] IL-6 can induce thrombocytosis through thrombopoietin,[9] and may induce ET. IL-6 may be a common link between MM and ET. Third, the treatment of one malignancy may lead to the development of a second malignancy. Both of our patients had a history of hydroxyurea use for several years. The sequential use of busulfan and hydroxyurea significantly increases the risk of second malignancies, and the risk of leukemia is slightly increased after treatment with hydroxyurea alone.[10] However, one study suggested that there is insufficient evidence of secondary leukemia or other malignancies in patients with ET using hydroxyurea alone.[11] The hypothesis of a second tumor secondary to hydroxyurea does not explain the coexistence of MM

combined with MPN at the time of initial diagnosis. The co-occurrence of these two malignant tumors may also be purely coincidental.

Because of its extremely low incidence, there are no standard treatment options for MM co-occurring with MPN, and the combined presence of two hematologic tumors makes treatment challenging. When MPN and MM coexist, the most aggressive malignancy of the two needs to be treated first. In most previous case reports, the treatment regimen primarily targeted MM. We used a DRd regimen to treat our first patient. After one course of treatment, the patient's leukopenia and anemia were significantly improved. High-dose melphalan combined with autologous peripheral blood hematopoietic stem cell transplantation is reportedly effective in controlling the disease in patients with MM combined with ET.[12] As previously reported,[13] the presence of *JAK2* mutation in our patients is presumed to have derived from persistent MPN, not from myeloma, as no studies have convincingly demonstrated the presence of *JAK2V617F* mutation in MM. The role of Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling in myeloma cell survival and proliferation has been demonstrated, and STAT3 signaling in MM is associated with survival and drug resistance.[14] In addition, STAT3 plays a key regulatory role in inducing and maintaining angiogenesis in the BM of patients with MPN. A phase I trial[15] demonstrated that the JAK inhibitor ruxolitinib can overcome refractoriness to lenalidomide and steroids in patients with relapsed/refractory MM, indicating the potential of JAK inhibitors as therapeutic options for patients with MM combined with MPN.

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Authors contribution

Qiuqing Xiang conducted the case arrangements and wrote the article; Bin Chu, Lei Shi, Yuan Chen, and Yutong Wang contributed to the diagnosis and treatment of the disease; Li Bao, Kai Sun, and Minqiu Lu were involved in the study design and helped draft the manuscript. All authors have read and approved the final draft of the manuscript.

Ethics statement

The study was conducted in accordance with the *Declaration of Helsinki*. The study was approved by the Beijing Jishuitan Hospital Ethics Committee. The ID is JST[2023] No. [014]-00. Written informed consent for treatment and genetic testing was obtained from the patients.

Data availability statement

The datasets used in the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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