Multiple myeloma secondary to acute lymphoblastic leukemia
A case report

Tonglin Hu, MS, Jianping Shen, MS, Wenbin Liu, MD, Zhiying Zheng, MD

Abstract
Rationale: Acute lymphoblastic leukemia (ALL) secondary to multiple myeloma (MM) is rare. Here we report a rare case of secondary ALL transformed from MM.

Patient concerns: A 64-year-old woman was diagnosed as MM IgG light chain type in 2001. She achieved complete remission after 2 cycles of therapy, and received maintenance therapy with thalidomide. The patient suffered from MM relapse in September 2011. Bone marrow examination showed that the percentage of primary lymphocytes was 59%, indicating ALL-L2 (Pre-B-ALL). The patient reached complete remission after 1 cycle of chemotherapy, and has been maintained for more than 6 years.

Diagnoses: Immunoophenotyping analysis revealed that the abnormal cell population accounted for approximately 66% which expressed HLA-DR, CD4, CD22, CD33, CD34, and cCD79a. These results indicated acute B lymphoblastic leukemia. Chromosome presented 47, XX, +5, −7, +19. Leukemia fusion gene analysis demonstrated positive EVI1 and negative IgH and TCR gene rearrangement.

Interventions: The patient accepted 1 cycle of VDCLP chemotherapy and reached complete remission, followed with consolidation therapies with VDCLP, MA, CAG and other chemotherapy regimens.

Outcomes: This patient has maintained CR1 of ALL for more than 6 years.

Lessons: Even secondary lymphoblastic leukemia has been rarely reported in patients with MM, we still need perform bone marrow examination, flow cytology, and gene tests, especially during maintenance therapy.

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CAG = cyclophosphamide, cytosine arabinoside, Granulocyte stimulating factor, CR1 = complete remission for the first time, ECT = emission computed tomography, L-Asp = L-asparaginase, MA = mitoxantrone, cytarabine, MDS = myelodysplastic syndrome, MLL = mixed lineage leukemia, MM = multiple myeloma, MRD = minimal residual disease, MRI = magnetic resonance imaging, MTX = methotrexate, PAD = pirarubicin, vancomycin, dexamethasone, STR = short tandem repeat, VDCLP = vincristine, pirarubicin, cyclophosphamide, L-asparaginase, dexamethasone.

Keywords: acute lymphoblastic leukemia, multiple myeloma

1. Introduction
Multiple myeloma (MM) is the malignancy of plasma cells. The clonal proliferation of myeloma cells in the bone marrow would cause bone pain or pathological fracture. At present, chemotherapeutic drugs for MM include, but not limited to, thalidomide, proteasome inhibitor, and hormone. MM secondary to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are mainly considered to be related to the use of alkylating agents. There are numerous reports of MM secondary to AML. However, a case of MM secondary to acute lymphoblastic leukemia (ALL) is rarely reported. In the present study, we report a patient with MM secondary to ALL and reviewed the related literature.

2. Case presentation
A 64-year-old woman had repeated back pain without obvious reasons approximately in 2001, and the pain could not be alleviated by antipyretic analgesics. She visited a local hospital and was diagnosed as MM IgG light chain type (ISS stage: Stage II, Type A) based on bone marrow biopsy, immunofixation electrophoresis, emission computed tomography (ECT) and lumbar magnetic resonance imaging (MRI). Then, she received 1 cycle of vincristine, darubicin, and dexamethasone (VAD) therapy and 1 cycle of vincristine, mitoxantrone and dexamethasone (VMD) therapy. The hematuria immunofixation electrophoresis result was negative, and bone marrow examination revealed myeloma cell fluctuation of 1.5% to 3%, which indicated complete remission. The patient was subsequently
treated with 5 cycles of VMD consolidation therapy and 2 cycles of improved M2 (cyclophosphamide, melphalan, prednisone, and vincristine) consolidation therapy. The cyclophosphamide accumulation was 1.2 g, while the melphalan accumulation was 64 mg, with which both bone marrow examinations revealed remission. The patient continued to take thalidomide as maintenance treatment until June 2007.

Due to intense back pain, the patient went to our hospital in September 2011. Bone marrow examination revealed that myeloma cells accounted for 15% of all cells (Fig. 1). ECT revealed that sacrum, lumbar 5, 1 to 4, thoracic 7, 8, and left sacroiliac bone metabolism were extremely active, indicating the possibility of metastases. Furthermore, IgG was 66 g/L, while IgE, IgD, and IgA levels were normal. Blood examination results were as follows: light chain kap: 85.6 g/L and lam: 185 g/L; creatinine: 68 umol/L; LDH: 245 U/L; blood calcium: 2.13 mmol/L; total protein: 79 g/L; globulin: 54 g/L; β2 microglobulin: 4.9 mg/L. Bone marrow examination revealed a myeloma cell fluctuation of 78.5%. Chromosome presented 46, XX. Serum immunofixation electrophoresis revealed IgG light chain type, and indicated MM relapse. The patient was treated with pirarubicin, vancomycin, dexamethasone (PAD) chemotherapy twice successively in our hospital. Bone marrow examination revealed a myeloma cell fluctuation of 0.5% to 1%, and the hematuria immunofixation electrophoresis result was negative, indicating that MM was close to complete remission. The patient went to our hospital for consolidation therapy in October 2012. Bone marrow examination demonstrated that the nucleated cell hyperplasia was extremely active (granulocyte-to-nucleated erythrocyte ratio = 0.4:1.0). Primitive cells accounted for 59%, which contained round cell bodies, a rich cytoplasm, visible vacuoles, and coarse aniline blue particles, regular nucleus, compact chromatin, 1 to 3 visible nucleoli, negative POX staining, and visible degraded cells, but there were no myeloma cells. The symptom of myeloid revealed ALL-L2 (Fig. 2). Immunophenotyping analysis revealed that the abnormal cell population accounted for approximately 66% of nucleated cells in the distribution area, in which CD45 was negative, and the side-scattered light was larger than the nucleated red blood cells. This abnormal cell population mainly expressed HLA-DR, CD4, CD22, CD33, CD34, and cCD79a, and the proliferation of myeloid was inhibited. These results indicated acute B lymphoblastic leukemia.

Figure 1. Bone marrow examination when the patient was admitted at our hospital in September 2011. Bone marrow smears were found in myeloma cells. (rui staining ×1000).

Figure 2. Bone marrow examination when the patient received consolidation therapy at our hospital in October 2012. Left: Bone marrow smears revealed primitive and naive lymphocytes (rui staining ×1000). Right: There were no brown black granules in the cytoplasm (POX staining ×1000).
Leukemia fusion gene analysis demonstrated positive EVI1 and negative IgH and TCR gene rearrangement. Furthermore, the patient was secondary, but not concurrent, ALL-L2 (former B type). Bone marrow examination was performed (12th of November 2012). Then, 1 cycle of VDCLP (vincristine, pirarubicin, cyclophosphamide, L-asparaginase, dexamethasone) chemotherapy was initiated on the 18th of October 2012. The results indicated that patient symptoms disappeared, and bone marrow and blood indexes recovered. Flow cytometry revealed that minimal residual disease (MRD) was negative, suggesting that patient response was CR1 complete remission for the first time (CR1).

The patient was discharged from the hospital after 1 additional cycle of VDCLP consolidation therapy. Then, the patient received 14 cycles consolidation therapy, as follows: MTX + L-ASP (methotrexate, L-asparaginase), mitoxantrone, cytarabine (MA), cyclophosphamide, cytosine arabinoside, granulocyte stimulating factor (CAG) and VDCLP consolidation therapy. She received 6-MP and MTX as a maintenance treatment. The bone marrow of the patient was monitored. MRD was negative, and at present, ALL has been sustained at CR1 for more than 5 years.

3. Ethics statement
As a case report with written consent, our hospital does not require formal ethical approval. Written informed consent was obtained from the patient and her husband for publication of this case report.

4. Discussion
Eighty-five percent of secondary leukemia patients receive alkylating agent treatment, and 65% of chemotherapy-induced leukemia is caused by melphalan, chlorambucil, and cyclophosphamide. The incidence of secondary leukemia in MM patients is 0.7% to 25%, which is 100 to 200 times higher than the incidence of leukemia in the normal population. Although acute leukemia-related treatment is common, ALL related treatment accounts for only approximately 12%. Among ALL related treatments, the use of alkylating agent accounted for only 0.5% to 1%. Recently, Tan et al reviewed a case series in which patients receiving lenalidomide maintenance therapy developed secondary ALL. Consistent with their report, the patient in the present study continued to take thalidomide as a maintenance treatment. The bone marrow of the patient was monitored. MRD was negative, and at present, ALL has been sustained at CR1 for more than 5 years.

In the present case, the MM (IgG type) patient was treated with multiple chemotherapy regimens, including alkylating agents, and developed ALL after 11 years. The cumulative amount of cyclophosphamide was 1.2g and the sum of melphalan was 64 mg. Although the chromosome karyotype of the patient was abnormal after conversion into ALL and IgH gene rearrangement was negative, it could not be confirmed whether MM and ALL developed from different clones due to the lack of results on chromosomes and bone marrow examination at the onset of MM.

The prognosis of leukemia is related to many factors, such as leukemia fusion gene, chromosome, immunophenotyping, and age. Leukemia fusion gene EVI1 is an oncogene, and its expression is associated with the acute change of AML and chronic myeloid leukemia (CML). The lifespan of EVI1-positive patients is significantly shorter than that of EVI1-negative patients. It has been reported that chromosome translocation may lead to the activation of EVI1, and chromosomal abnormalities may be correlated to the use of alkylating agents. Alkylating agents with anti-tumor effects induce chromosome mutation, especially Chromosomal 5 and 7 abnormalities, leading to the activation of oncogene Ras and the inactivation of tumor suppressor gene p53, as well as uncontrolled cell proliferation and leukemia. Reddi and Lu reported that the abnormal Chromosome 5 and 7 were related to the use of multiple chemotherapy programs, especially melphalan and cyclophosphamide. Therefore, it could be speculated that the use of alkylating agents in this patient might be 1 cause of the abnormal EVI1 gene on Chromosome 5 and 7, leading to the occurrence of ALL.

CD34 is a marker of the poorly differentiated stage of acute leukemia cells, and a high CD34 expression indicates low tumor cell differentiation, less sensitivity to chemotherapy and poor prognosis. Myeloid antigen CD33 is an indicator of poor prognosis for ALL. The patient in the present case had a high expression of HLA-DR, CD34, and CD33, which suggested that the patient had ALL with poor prognosis. B-ALL can be divided into 4 hypotypes: Pro-B-ALL, c-ALL, Pre-B-ALL, and Mature-B-ALL. The CR rate of B-ALL and cell differentiation were negatively correlated. The remission rate of Pro-B-ALL was the highest, followed by c-ALL, Pre-B-ALL, and Mature-B-ALL. The patient in the present case was older than 50 years old, and developed secondary ALL, which was Pre-B-ALL with Chromosome 5 and 7 abnormalities and positive CD34 and EVI1 expression, all of which suggests poor prognosis. However, the patient reached complete remission after 1 cycle of VD-CLP chemotherapy, and no recurrence occurred after consolidation therapies with VDCLP MA, CAG, and other chemotherapy regimens. ALL (CR1) has been maintained for more than 5 years until now.

5. Conclusion
The present case suggests that we should pay attention to MM secondary to ALL and take proper measure of treatment.

Acknowledgment
This study was supported by the General Project Funds from the Health Department of Zhejiang Province (2015KYB264)

Author contributions
Conceptualization: Zhiying Zheng
Data collection and drafting of the original article: Tonglin Hu
Development of the idea and editing of the final draft: Zhiying Zheng.
Development of the idea and the treatment plan: Wenbin Liu.
Formal analysis: Wenbin Liu.
Funding acquisition: Jianping Shen.
Investigation: Tonglin Hu, Jianping Shen, and Wenbin Liu.
Methodology: Wenbin Liu and Zhiying Zheng.
Project administration: Jianping Shen.
Project administration: Tonglin Hu, Jianping Shen, Wenbin Liu, and Zhiying Zheng.
Resources: Tonglin Hu, Jianping Shen, Wenbin Liu, and Zhiying Zheng.
Validation: Jianping Shen.

References
[1] Castillo JJ, Gertz MA. Secondary malignancies in patients with multiple myeloma, Waldenstrom macroglobulinemia and monoclonal gammopathy of undetermined significance. Leuk Lymphoma 2017;58:773–80.
[2] Junxun L, Junru L, Meilan C, et al. Three patients with multiple myeloma developing secondary lymphoblastic leukemia: case reports and review of the literature. Tumori 2016;102:5131–6.
[3] Pszcz J, Boluk L, Cichocka E, et al. Secondary acute lymphoblastic leukaemia in a multiple myeloma patient. Contemp Oncol (Pozn) 2012;16:593–5.
[4] Tan M, Fong R, Lo M, et al. Lenalidomide and secondary acute lymphoblastic leukemia: a case series. Hematol Oncol 2017;35:130–4.
[5] Oken MM, Harrington DP, Abramson N, et al. Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma: results of Eastern Cooperative Oncology Group Study E2479. Cancer 1997;79:1561–7.
[6] Ishizawa S, Slovak ML, Popplewell L, et al. High frequency of pro-B acute lymphoblastic leukemia in adults with secondary leukemia with 11q23 abnormalities. Leukemia 2003;17:1091–5.
[7] Leone G, Voso MT, Sica S, et al. Therapy related leukemias: susceptibility, prevention and treatment. Leuk Lymphoma 2001;41:255–76.
[8] Lau LG, Tan LK, Koay ES, et al. Acute lymphoblastic leukemia after tandem autologous stem cell transplantations for multiple myeloma. Leukemia 2005;19:299–301.
[9] Ueda K, Yamamoto G, Shinohara A, et al. Early onset of acute lymphoblastic leukemia with MLL rearrangement after autologous stem cell transplantation for multiple myeloma. Ann Hematol 2009;88:813–4.
[10] Igarashi N, Chou T, Hirose T, et al. Donor cell-derived acute lymphocytic leukemia after allogeneic stem cell transplantation for multiple myeloma. Int J Hematol 2009;90:378–82.
[11] Groshchel S, Lughart S, Schlenk RF. High EVI1 expression predicts outcome in younger adult patients with acute myeloid leukemia and is associated with distinct cytogenic abnormalities. Clin Oncol 2010;28:2101–7.
[12] Reddi DM, Lu CM, Fedoriw G, et al. Myeloid neoplasms secondary to plasma cell myeloma: an intrinsic predisposition or therapy-related phenomenon? A clinicopathologic study of 41 cases and correlation of cytogenetic features with treatment regimens. Am J Clin Pathol 2012;138:555–66.
[13] Peters JM, Ansari MQ. Multiparameter flow cytometry in the diagnosis and management of acute leukemia. Arch Pathol Lab Med 2011;135:44–54.
[14] Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 2008;111:4477–89.