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Case Report

Acute Myeloid Leukemia M2 Transformed into M6 after the Treatment of Azacitidine Combined with Venetoclax: A Case Report

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Abstract

It is uncommon for acute myeloid leukemia to have a phenotypic transformation. Conversion from acute myeloid leukemia-M2 to acute myeloid leukemia-M6 is even rarer. This study reported an 82-year-old man with initial diagnosis of acute myeloid leukemia-M2. After three cycles of azacitidine combined with venetoclax chemotherapy, the bone marrow smear showed M6 of acute myeloid leukemia. We believe that the probable reasons are as follows: 1. The change of hematopoietic microenvironment causes the damage of erythrocyte system. 2. There were two groups (M2 and M6) of tumors in the patients. In the early stage, the abnormal of erythrocytic series was suppressed and failed to be reflected. After chemotherapy, the erythrocytic series was less inhibited and its abnormality was expressed. 3. The repeated use of chemotherapy drugs causes cell abnormalities that lead to lineage switch in acute myeloid leukemia.

INTRODUCTION

Acute myeloid leukemia (AML) is a malignant disease of myeloid hematopoietic stem cells. The disease is characterized by abnormal proliferation of myeloid hematopoietic stem cells, cell differentiation blocked and apoptosis inhibition [1]. The patients of AML have heterogeneity at the molecular genetic level including gene mutations or abnormalities in the expression of certain genes. Therefore, it was classified M1-M7 according to the distinguish of morphology. The number of myeloblast and promyelocytic granulocytes increased significantly in AML-M2. However, patients with AML-M6 have an abnormally large hyperplasia of the erythrocyte line. M6 is a rare subtype of acute myeloid leukemia and accounts for less than 5% of all AML diseases [2]. In addition, the prognosis of AML-M6 is very poor.

This case reported an 82 years old male patient who was diagnosed AML-M2 with DNMT3A mutation (45.75%), TP53 mutation (44.29%), and MLL mutation (59.65%).

He was not suitable for standard induction therapy of AML with daunorubicin and Ara-C (DA) 3+7 though assessment, therefore, he accepted a treatment of azacitidine 110 mg subcutaneous injection of day 1-7 combined with venetoclax 50mg oral every day. The bone marrow (BM) smear and BM flow cytometry (FCM) of the patient indicated AML M6 instead of AML-M2 after he had completed three cycles of chemotherapy.

CASE PRESENTATION

A 82-year-old Chinese man was admitted to the 70 Department of Hematology of West China Hospital, Sichuan University (Chengdu, China) due to shortness of breath and weakness for one month in January, 2020. The preliminary laboratory evaluation revealed a hemoglobin (HB) concentration of 69g/L (normal range, 120-160 g/L), a white blood cell (WBC) count of 2.53×109 cells/L (normal range, 4-10×109 cells/L), a platelet (PLT) count of 67×109 cells/L (normal range, 100-300×109 cells/L) and an immature granulocyte count of 0.18×109 cells/L (normal range, 0 cells/L). BM smear showed that the percentage of myeloblast was 26% which indicated the diagnosis of AML-M2. BM biopsy presented that the proliferation of bone marrow hematopoietic cells was active, mainly with granulocyte hyperplasia, and that the number of immature granulocytes increased and megakaryocytes revealed polymorphic abnormalities. The BM FCM showed that the original cells occupied about 13% of the nuclear cells, expressing cluster of differentiation (CD)34, CD117,

CD123, CD13, CD33 (partially positive), CD56 (distributed positive), and human leukocyte antigen-DR (HLA-DR), without expressing CD14, CD64, CD5, CD7 and CD19. Abnormal progenitor granulocytes accounted for 13% of the nuclear cells, and the granulocyte phenotype expressing CD13/CD16 was abnormal in the next stage. Karyotype of bone marrow was 75~90, XXYY, inc[cp20]. The gene mutational analysis revealed that DNMT3A mutation (45.75%), TP53 mutation (44.29%), and MLL mutation (59.65%).

The patient accepted a treatment of azacitidine associated with venetoclax, one of the BCL-2 inhibitors. The specific treatment is 110mg azacitidine subcutaneously injected d1-7 with 100mg d1, 200mg d2, and 400mg d3-28 venetoclax from 20th February 2020. During this time, he suffered from lung infections and was treated with drugs such as voriconazole. Because voriconazole is a potent CYP3A 93 inhibitor, venetoclax was reduced to 50mg a day from March. And then the patient accepted respectively the second and the third cycle's chemotherapy from azacitidine and venetoclax on 30th March 2020 and on 10th May 2020. On 20th April 2020, routine blood examination indicated that a WBC count of 1.53 ×109 cells/L, a PLT count of 90×109 cells/L and a HB concentration of 84g/L with 23/50% neutrophilic segmented granulocyte (NSG). The BM smear showed that the hyperplasia of hematopoietic cell was not active, and no myeloblast was detected. BM FCM revealed that abnormal progenitor granulocytes, partly expressing CD56, ac101 counted for 3.9% of the nuclear cells.

On 9th June 2020, the patient felt short of breath and weak after activity with purpura in his skin after he had completed three cycles of chemotherapy. His blood samples showed a WBC count of 0.99×109 cells/L, a PLT count of 7×109 cells/L and a HB concentration of 54g/L with 45.5 % NSG and no myeloblast. After blood transfusion and leukocyte-raising treatment, the patient's symptoms eased slightly. The analysis of BM smear indicated the ratio of granulocytes to nucleated red blood cells was 0.01:1. The severe dysplasia of the erythrocyte series accounted for 93% and 60.5% were original erythroblastic. There are 5 megakaryocytes and scattered platelets. FCM of BM indicated AML-M6 that the proerythroblast, expressing CD117, CD36, CD71, GlyA, account for 60% of nuclear cells. The patient was considered to be with AML-M6 instead of AML M2 according to the BM assessment.

DISCUSSION

The patient transformed from acute myeloid leukemia type M2 to M6 within six months. Such cases are rare in the reported literature. 116 As for the lineage switch of leukemia, most of the literature reports the transformation between acute myeloid leukemia and acute lymphocytic leukemia. Lee HR reported a case of biphenotypic acute leukemia transformed from AML in 2008 [3]. There are also reported cases of conversion from AML to T cell/myeloid mixed phenotype acute leukemia [4] and to mixed phenotype acute leukemia, B/Myeloid [5]. However, it is rare of phenotypic transformation between AML. Conversion from acute myeloid leukemia subtype M2 to M6 is less common. In 2001, a Chinese study reported that a 62-year-old woman converted from AML M2 to AML-M6. In this paper, the author considered the possibility that this female patient had acute erythroleukemia M6 secondary to acute myelogenous leukemia M2 [6]. The 62-year-old female patient achieved a complete remission (CR) of more than 1 year after chemotherapy and other supporting treatments. Compared with the woman, the 82-year-old patient received different treatments and he did not obtain CR from AML. We propose the following reasons for the lineage switch of acute myeloid leukemia in this case.

Firstly, the patient's erythrocytic series may be damaged because of changes in the hematopoietic microenvironment during the treatment. The induced causes need to be further explored. In the study of cell heterogeneity and lineage transformation induced by the plasticity of leukemia cells, Dorantes et al mentioned that the abnormal function of microenvironmental signals may guide phenotypic transformation of leukemia by regulating the plasticity of leukemia cells [7]. Chemotherapy drugs have certain effects on the bone marrow microenvironment. It is summarized that the mutual adaptation of hematopoietic stem cells and bone marrow microenvironment, as well as the mutual regulation of various cytokines, molecular pathways and various molecules together maintains the stability of hematopoietic [8]. Abnormal hematopoiesis may result after homeostasis is affected. In this cace, the patient received a standard dose of azacitidine for chemotherapy. At the same time, he also used venetoclax (50mg per day). We consider that the chemotherapy drugs he used may affect the BM microenvironment and then may damage the erythrocytic series. However, the specific mechanism of whether azacitidine with venetoclax affecting the hematopoietic microenvironment is unclear and needs further confirmation.

Furthermore, it is also possible that there were two tumor groups, M2 and M6, achieved clone evolution. At the initial stage of the disease, the granulocytes were the main malignant clones and the red lineages were subclasses which were not obvious and were difficult to detect by conventional methods. As the treatment proceeded, the sensitive granulocyte clones were killed. While the erythron clones were not sensitive to the treatment and were gradually screened out to be the dominant clones. Tang et al speculated the cause of lineage switch in a case of acute monocytic leukemia to acute erythroleukemia. They suggested that there may be two kinds of anomalies at the same time. In the early stage of the disease, the abnormal expression of monocytic series was obvious. But it was not apparent that the erythrocytic series had abnormal expression.

Chemotherapy inhibited the primary monocytic series. However, the erythrocytic series had little effect and increased significantly after chemotherapy. Therefore, the later stage of the disease is mainly expressed as erythrocytic series anomaly [9]. The initial laboratory examination of the patient in this case was consistent with the diagnosis of AML M2. After three cycles of chemotherapy, the M2 tumor group was inhibited. At this time, the damage of the erythrocytic series was reflected, and the M6 tumor group was expanded.

In addition, we speculate that the patient may have cell abnormalities caused by repeated use of chemotherapy drugs, which may lead to the lineage switch of acute myeloid leukemia. It has been mentioned in a literature that AML-M6 may be secondary to prior chemotherapy or immunosuppression for a variety of malignant and nonmalignant diseases [10]. Thrombocytopenia was found to be a common hematologic toxicity in a study exploring the treatment with azacitidine in

elderly patients with acute myeloid leukemia [11]. In a study of the safety and preliminary efficacy of venetoclax combined with decitabine or azacitidine in elderly patients with acute myeloid leukemia, an adverse event of neutropenia count reduction (6 patients) was reported in the group of venetoclax combined with azacitidine (22 patients) [12]. Andrew et al., also reported thrombocytopenia in venetoclax combined with azacitidine for elderly patients with acute myeloid leukemia [13]. These may explain the sharp decline of platelets and granulocytes in this patient at the end of treatment. Using azacitidine and venetoclax to treat AML may cause some adverse cellular responses, which may induce lineage switch of acute myeloid leukemia. The mechanism of this supposes needs further study.

CONCLUSION

In summary, as for this patient, the cause of phenotypic transformation of AML has not been confirmed. It needs further exploration. This rare case is a supplement to the cases of lineage switch in acute myeloid leukemia. And it enriches thoughts on the classification and medication of leukemia for clinicians in the course of diagnosis and treatment.

REFERENCES

1. Grove Carolyn S, Vassiliou George S. Acute myeloid leukaemia: a paradigm for the clonal evolution of cancer. Dis Model Mech. 2014; 7: 941-51.
2. Arber DA, Brunning RD, Orazi A, Peterson L, Thiele J, Lee Beau MM. Acute myeloid leukemia, not otherwisw specified. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue. IARC; Lyon, France: 2008; 130-139.
3. Lee Hye Ryun, Kang Seong Ho, Kang Hyoung Jin, Shin Hee Young, Ahn Hyo Seop, Kim Hyun Kyung, et al. Lineage switch from acute myeloid leukemia to biphenotypic acute leukemia with acquisition of Philadelphia chromosome. Cancer Genet Cytogenet. 2008; 184: 124-6.
4. Hanley Brian P, Yebra-Fernandez Eva, Palanicawandar Renuka, Olavarria Eduardo, Naresh Kikkeri N. Lineage switch from acute myeloid leukemia to T cell/myeloid mixed phenotype acute leukemia: First report of an adult case. Am J Hematol. 2018; 93: 395-397.
5. Nomani Laila, Cook James R, Rogers Heesun J. Very rare lineage switch from acute myeloid leukemia to mixed phenotype acute leukemia, B/Myeloid, during chemotherapy with no clonal evolution. Int J Lab Hematol. 2019; 41: 86-88.
6. Zhao Huifen. Acute myelogenous leukemia M2 was transformed into acute erythroleukemia M6 in a case. Chinese Medical Journal of Metallurgical industry. 2001; 18: 261.
7. Elisa Dorantes-Acosta, Rosana Pelayo. Lineage switching in acute leukemias: a consequence of stem cell plasticity?. Bone Marrow Res. 2012; 2012: 406796.
8. Du Hua, Shi Yingxu. Regulation of hematopoietic stem cell fate by bone marrow microenvironment. Chinese Journal of Tissue Engineering Research. 2015; 19: 2283-2290.
9. Tang Jing, Meng Li, Tang Yi, He Li, Bu Yajing, et al. A Case Report: Acute Monocytic Leukemia Switching to Acute Erythroid Leukemia and Review of the Literature. Progress in Modern Biomedicine. 2012; 12: 6473-6476.
10. Killick S, Matutes E, Powles RL, Min T, Treleaven JG, Rege KP, et al. Acute erythroid leukemia (M6): outcome of bone marrow transplantation. Leuk Lymphoma. 1999; 35: 99-107.
11. Santhosh K. Sadashiv, Christie Hilton, Cyrus Khan, James M Rossetti, Heather L Benjamin, Salman Fazal, et al. Efficacy and tolerability of treatment with azacitidine for 5 days in elderly patients with acute myeloid leukemia. Cancer Med. 2014; 3: 1570-1578.
12. Courtney D DiNardo, Keith W Pratz, Anthony Letai, Brian A Jonas, Andrew H Wei, Michael Thirman, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018; 19: 216-228.
13. Andrew H Wei, Stephen A Strickland Jr, Jing-Zhou Hou, Walter Fiedler, Tara L Lin, Roland B Walter, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients with Acute Myeloid Leukemia: Results From a Phase Ib/II Study. J Clin Oncol. 2019; 37: 1277-1284.

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