First reported case of acute megakaryoblastic leukemia successfully treated with decitabine and venetoclax combined with imatinib

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Case Report

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Abstract

Acute megakaryocytic leukemia (AMKL) is a rare type of acute myeloid leukemia (AML), which is characterized by its effect on megakaryocytes in bone marrow. Despite standard doses of anthracycline plus cytarabine based regimen, AMKL is notorious for its poor prognosis. With the continuous development of targeted drugs, the choice of chemotherapy regimens for AML patients has been gradually enriched. However, as far as we known, there is little data with this regimen in AMKL with decitabine and Bcl-2 inhibitor combined with imatinib. Herein, we reported the first case of adult AMKL with BCR-ABL positive successfully treated with decitabine and venetoclax combined with imatinib.

Background

Acute megakaryocytic leukemia (AMKL), known as M7 in the FAB classification, is an uncommon subtype of acute myeloid leukemia (AML), accounting for about 10% in children while only 0.6% in adults.[1, 2] In adult cases, AMKL tends to occur in people in their 50s and 60s. [3] The diagnosis of AMKL is based on the bone marrow where the proportion of blasts is 20% or greater, of which ≥ 50% are of the megakaryocyte lineage.[4]

Immunohistochemistry stains and flow cytometry have greatly improved the diagnostic efficacy of AMKL. In terms of immunophenotype, AMKL blasts usually show negativity for myeloperoxidase (MPO) and CD34, while positivity for CD13, CD33, CD41, CD61 and factor VIII.[5] Moreover, it is of great significance to perform molecular biology and karyotype analysis because AMKL is often associated with particular alternations and complex karyotype. In adult AMKL, the most common abnormalities are inv(3)(q21;126), t(9;22)(q34;q11) and aberrations of chromosome 5 and 7.[6, 7]

Adult AMKL can be further classified as primary or secondary, but in general, regardless of the type, the prognosis is poor, with the median overall survival of 10 months.[8] This poor outcome suggests that new and effective treatment regimens are urgently needed. Herein, we describe the clinical case of a 56-year-old male who was diagnosed in our hospital with AMKL, which was the first case of adult AMKL with BCR-ABL positive successfully treated with decitabine and venetoclax combined with imatinib.

Case Report

A 56-year-old man was admitted to our hospital at the beginning of June 2020 because of repeated fever for one month. The patient complained of repeated fever in the past month, with the temperature mostly around 38°C, and the temperature usually dropped in the middle of the night. What's more, fever was accompanied by no symptoms other than a mild headache.

Blood routine examination revealed pancytopenia in the patient (white blood cell counts $3.31*10^9$/L, 54.7% neutrophil, 26.9% lymphocytes, 17.8% monocytes; hemoglobin 84g/L; platelets $67*10^9$/L). Coagulation studies showed the international standardized ratio (INR) (1.21) and fibrinogen (6.15)

increased, the others including thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (APTT) were normal. Ferritin rose to 2,931.94 ng/ml. Lactate dehydrogenase (LDH) was slightly up to 582 U/L. In addition, we screened some infectious diseases and identified common bacteria, fungi, viruses and special pathogens such as Mycobacterium tuberculosis in blood, urine, feces, cerebrospinal fluid and alveolar lavage fluid specimens.

All the evidence pointed to blood system disorder, so we performed a bone marrow puncture and refined the positron emission tomography / computed tomography (PET/CT). Pathological hematopoiesis was found in the patient's first bone marrow smear (Fig. 1a), and the flow cytometry (FCM) revealed that abnormal myeloid cells accounted for 5.84%, with CD117, CD34, CD33, CD13 and HLADR positive (Fig. 2a), indicating myelodysplastic syndrome (MDS). Immunohistochemistry showed MPO(-), CD138(-), CD235(+), CD117(-), CD34(+), CD19(-), CD61(+). PET/CT found that 18F-flurodeoxyglucose (18F-FDG) metabolism in the scanning area of the medullary cavity was diffusely increased; liver was not large, 18F-FDG metabolism was slightly increased; spleen was enlarged, 18F-FDG metabolism was increased, suggesting hematological disease. We changed the site and then performed bone marrow puncture again. Bone marrow smear showed 6% of primitive lymphoid cells and 1% of phagocytic reticular cells (Fig. 1b). FCM found abnormal myeloid cells accounted for 6.71%, with CD117, CD34, CD33, CD13, HLADR and CD38 positive (Fig. 2b). Bone marrow biopsy revealed slightly lower hematopoietic hyperplasia, and immunohistochemical staining results were the same as the first time. On June 23th, we performed a third bone marrow puncture. This report suggested that the proportion of primitive megakaryocytes increased to 20.5%, which means the diagnosis of AMKL was made (Fig. 1c, 1d). FCM indicated abnormal myeloid cells accounted for 11.53%, with CD117, CD34, CD33, CD13, HLADR, CD123, CD61, CD41, CD42b and CD36 positive (Fig. 3). Chromosomal analysis with G-banded karyotype of bone marrow cells showed 45, XY, del(5)(q21q34),-7[4]/46,sl,del(3)(q25),+mar[1]/46,sdl,del(2)(p21)[2]/46,XY[3] (Fig. 4). Fluorescence in situ hybridization (FISH) and real time polymerase chain reaction (RT-PCR) confirmed that BCR/ABL was positive.

Based on the above information, the patient was currently diagnosed with AMKL (MDS transformation) and hemophagocytic lymphohistiocytosis. After the internal discussion in the department and the consent of the patients, we selected decitabine combined with Bcl-2 inhibitor for the induction chemotherapy of the patients. The specific plan was as follows: decitabine 38 mg d1-5; venetoclax 100 mg d1, 200 mg d2, 400 mg d3-28. Considering that the patient was positive for BCR/ABL fusion gene, oral imatinib was added at 400 mg/day for targeted therapy. During the treatment, antiemetic, gastric protection, blood component transfusion and other symptomatic support treatment were provided. After that, the patient's body temperature gradually stabilized, and the complete blood count (CBC) increased. After the general condition improved, the patient was discharged.

At the end of the first course of treatment, the patient achieved clinical and bone marrow remission, but had a hemoglobin of 56g/ L.

Comprehensive assessment was partial remission (PR). Thankfully, the patient achieved complete remission (CR) after the second course of chemotherapy with the same regimen and without any serious adverse events (CR was defined as < 5% blast cells in bone marrow, normal hematopoiesis, the absence of blasts cells in the peripheral blood and disappearance of extramedullary infiltration) (Fig. 5). What's more, RT-PCR showed that the M-BCR/ABL positive rate was 35% at the time of diagnosis, decreased to 13% after the second chemotherapy, and decreased to 0.024% after the third chemotherapy. After the third chemotherapy with the same regimen, the patient remained CR. However, after the fourth round of chemotherapy, the patient developed severe myelosuppression (white blood cell counts $0.65*10^9$/L, neutrophil $0.22*10^9$/L; hemoglobin 89g/L; platelets $24*10^9$/L). Then came a lung infection. After symptomatic treatment, the CBC increased and the lung infection gradually improved (white blood cell counts $5.7*10^9$/L, neutrophil $4.42*10^9$/L; hemoglobin 90g/L; platelets $97*10^9$/L).

To date, the patient has received a total of four cycles of chemotherapy and more than 10 months had elapsed between diagnosis and the last follow-up. We recommend that patients undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT) after first achieving CR. However, the patient rejected the offer because of the lack of donors, long waiting times and the huge cost.

Discussion

Adult AMKL is further divided into primary and secondary with both of them being very rare, and the latter is usually transformed by the progression of MDS[9–12], chronic myeloid leukemia (CML)[13–15], Essential thrombocythemia (ET) [16–18]and chronic idiopathic myelofibrosis (CIMF)[15, 19]. The patient had no previous history of CML. Combined with the results of several bone marrow tests, we consider this case to be secondary AMKL transformed from MDS.

As mentioned above, AMKL diagnosis is based on the bone marrow where the proportion of blasts is 20% or greater, of which ≥ 50% are of the megakaryocyte lineage. There are several difficulties. First, bone marrow tests are not always feasible because patients with AMKL often experience "dry tap" during bone marrow puncture. Therefore, multiple, multi-site bone marrow puncture is needed. Second, the diagnosis of AMKL needs to be differentiated from other diseases such as acute panmyelosis with myelofibrosis (APMF) and megakaryocytic blast phase of CML[20, 21]. The clinical features, morphologic and cytogenetic findings help in the identification and distinction of AMKL from other diseases. In this case, a definitive diagnosis was made after three bone marrow punctures. For the first time, the material was poor, which may be related to excessive fibrosis induced by megakaryocytes.

The standard treatment for AMKL is the same as that for AML other than acute promyelocytic leukemia (APL), which is mainly divided into induction regimen and consolidation therapy. The former included anthracycline for 3 days and cytarabine for 7 days. Nevertheless, the prognosis for adult AMKL remains extremely poor with a median overall survival of 10 months. In view of the poor prognosis, AMKL is considered to be an indication for allo-HSCT[22]. Allo-HSCT after CR is a much better option for adults AMKL as post-remission than conventional consolidation chemotherapy for the disease-free survival

(DFS) at 3 years was 46%. However, in the recent years, different opinions have emerged. Studies have indicated that treatment-related mortality for allo-HSCT in AMKL is lower in children and as high as 26% in adults.[23] In general, it is still considered that adult AMKL should undergo allo-HSCT after the first CR to achieve a better prognosis. Unluckily, the patient in this case did not ultimately accept this recommendation for several reasons such as the lack of donors, long waiting times and the huge cost.

As the mechanism of the disease continues to be explored, more and more new drugs appear, which brings new hope to many cancer patients, including AMKL patients. The advent of the era of targeted therapy provides more new options for the treatment of AMKL. The Bcl-2 protein family is one of the core regulatory mechanisms of apoptosis, which can receive and transmit internal or external environment stress intracellular signal, such as DNA damage, oncogene activation and endoplasmic reticulum stress excessive stress. Overexpression of Bcl-2 is a characteristic of many hematology malignancies. As far as we known, there is little data with this regimen in AMKL with decitabine combined with a Bcl-2 inhibitor. In this case, we chose decitabine combined with Bcl-2 inhibitor. Moreover, we noticed that the patient had positive BCR-ABL, which is usually present in CML. Thus, oral imatinib was added at 400 mg/day for targeted therapy. Such a regimen might seem radical, but with modern combination chemotherapy with small molecule-based therapy and cellular therapies, the prognosis for patients may improve dramatically. During this period, the patient experienced bone marrow suppression after chemotherapy, but the situation improved after symptomatic and supportive treatment such as blood transfusion and anti-infection. Now the patient has undergone four cycles of chemotherapy, followed up for more than 10 months, and is generally in good condition.

We are pleased to see that there are many other new treatments for AMKL available recently. Normally, megakaryocytes can skip late mitosis and go straight to be polyploid, but leukemic megakaryocytes cannot[24]. Recent studies have validated Aurora Kinase A (AURKA) potential as a therapeutic target. AURKA is a negative regulator of polyploidization. Wen et al. demonstrated that MLN8237 could potent anti-AMKL activity by inducing polyploidization as a selective proteasome inhibitor of AURKA kinase.[25] In addition, other inducers of polyploid differentiation have also attracted the attention of researchers.[26] Furthermore, a number of targets have also been found to increase sensitivity to chemotherapeutic agents.[27–30]

Finally, this is only one case report with its limitations. Long follow-up and more cases are needed to confirm the effectiveness of our regimen.

Declarations

Ethics approval and consent to participate

Informed consent was obtained in this case, and protocols were approved by the scientific ethical committee of our hospital.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

Wanzhuo Xie designed the study and provided the feedback. Huafei Shen, Xiaolong Zheng and Yuanfei Shi collected the clinical data and collected the related literature. Huafei Shen, Xiaolong Zheng and Yuanfei Shi also drafted the manuscript and figures. Jie Jin edited the manuscript. All authors read and approved the final manuscript.

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Figures

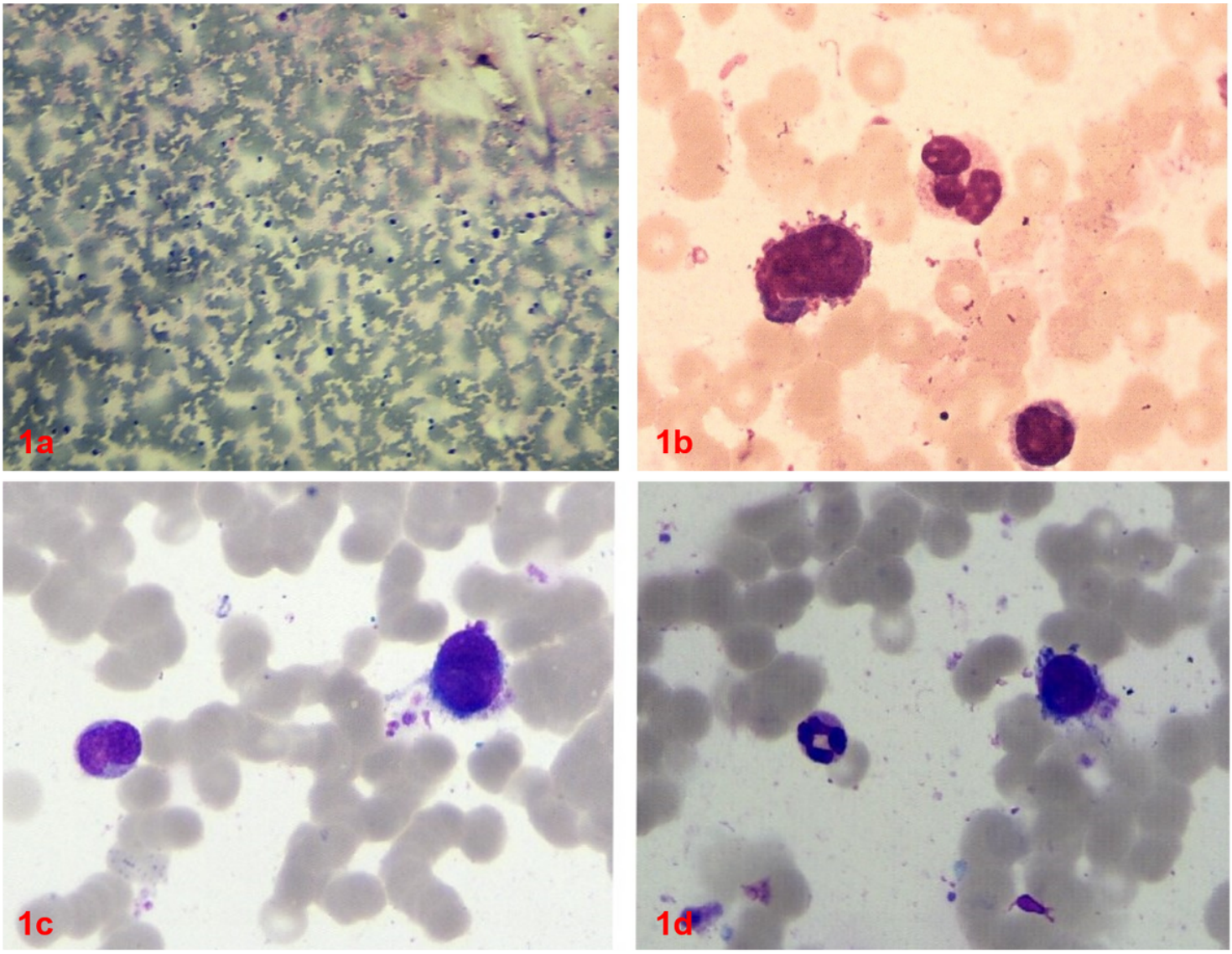

Figure 1

1a The first bone marrow cytology examination on June 9th: Poor sampling. Neutrophil alkaline phosphatase (NAP) positive rate 18%, integral 20 points (The reference range is 30-50% and the integral is 50-80). POX(-), SB(-), NSE(-), NAF is not color, PAS(-), SE(-). 1b The second bone marrow cytology examination on June 16th: Smear showed that the proportion of primitive lymphoid cells accounted for 6% and phagocytic reticular cells accounted for 1%. POX(-), SB(-), NSE(-), NAF is not color, PAS(-), SE(-). 1c, 1d The third bone marrow cytology examination on June 23rd: The proportion of naive cells similar to protomegakaryocytes increased by 20.5%, suggesting the possibility of AMKL. POX(-), SB(-), NSE(-), NAF is not color.

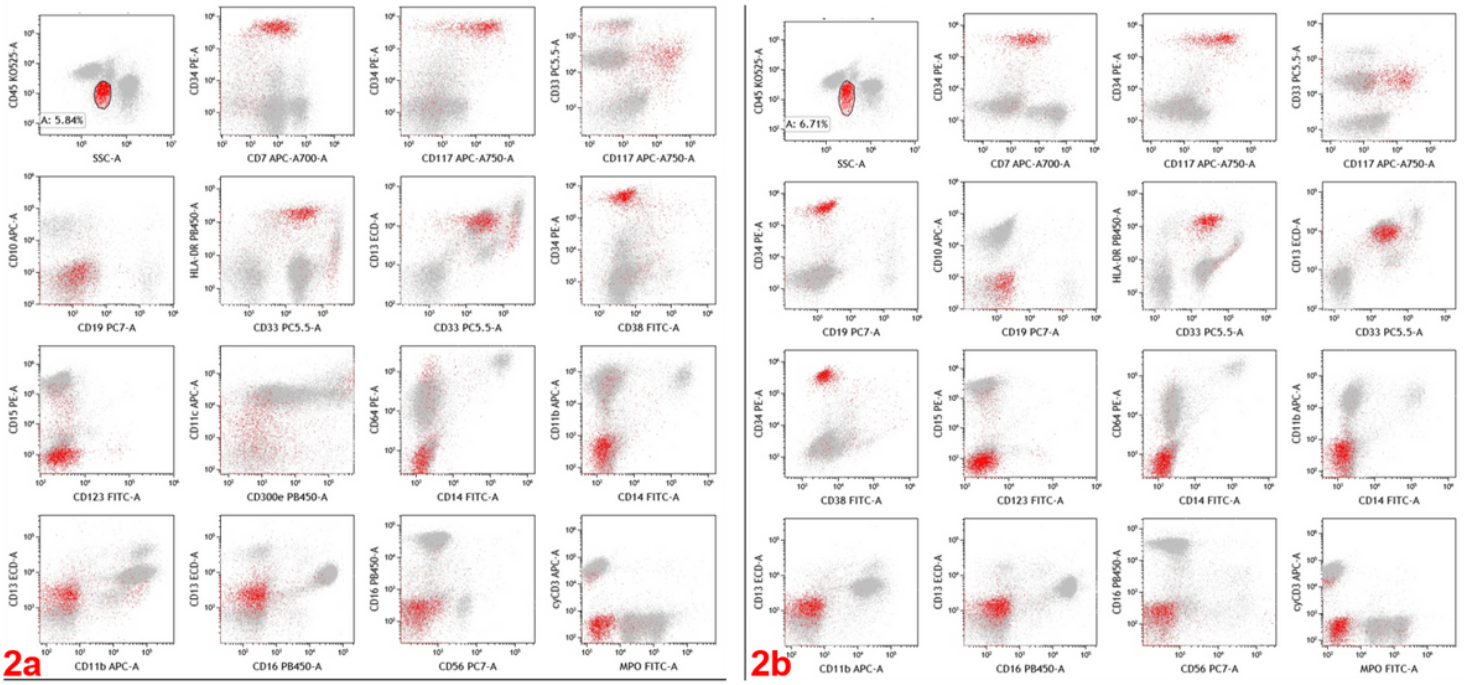

Figure 2

2a The first FCM on June 15th revealed that abnormal myeloid cells accounted for 5.84%, with CD117, CD34, CD33, CD13 and HLADR positive. 2b The second FCM on June 19th found abnormal myeloid cells accounted for 6.71%, with CD117, CD34, CD33, CD13, HLADR and CD38 positive.

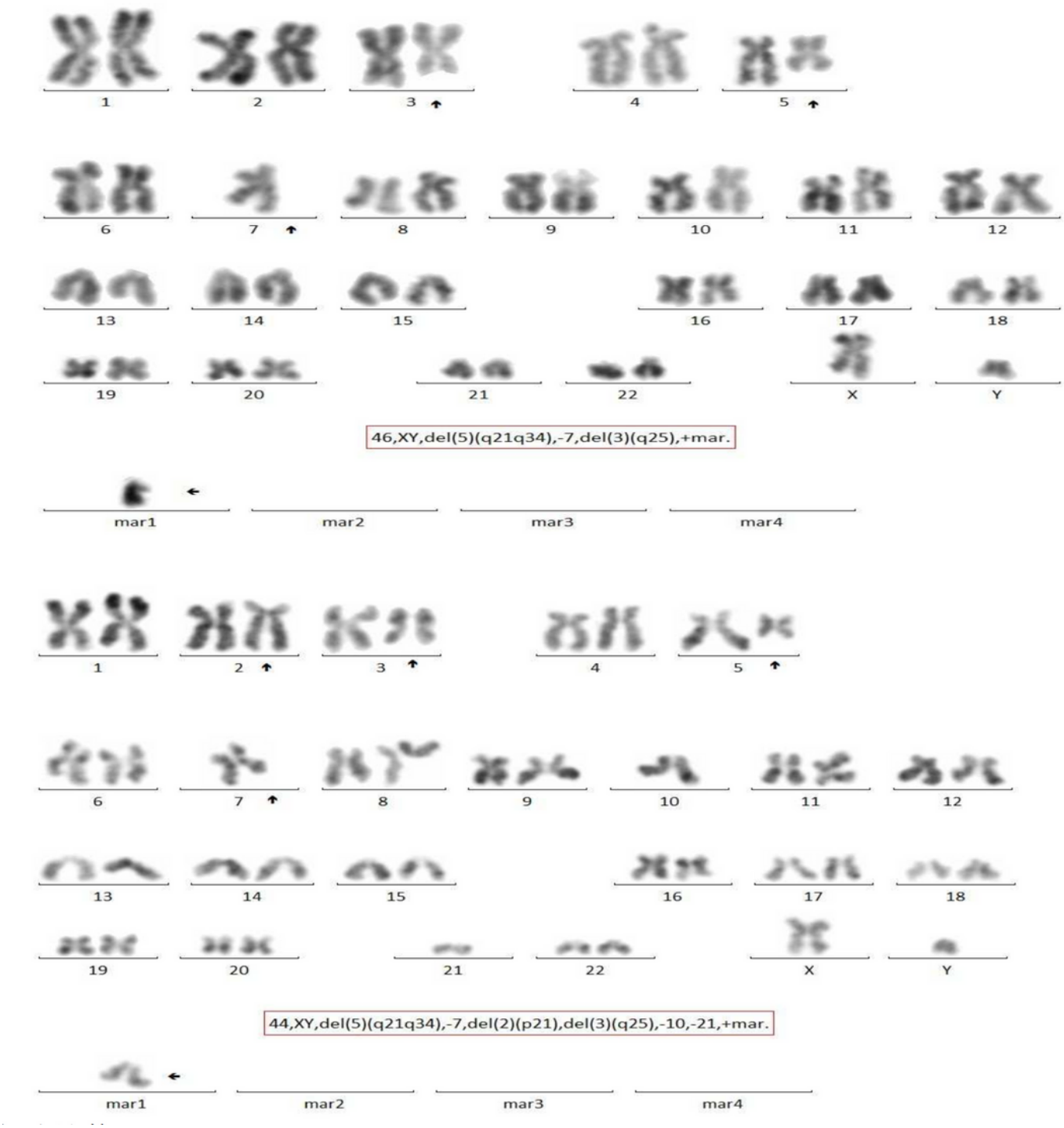

Figure 3

The third FCM on June 26th indicated abnormal myeloid cells accounted for 11.53%, with CD117, CD34, CD33, CD13, HLADR, CD123, CD61, CD41, CD42b and CD36 positive.

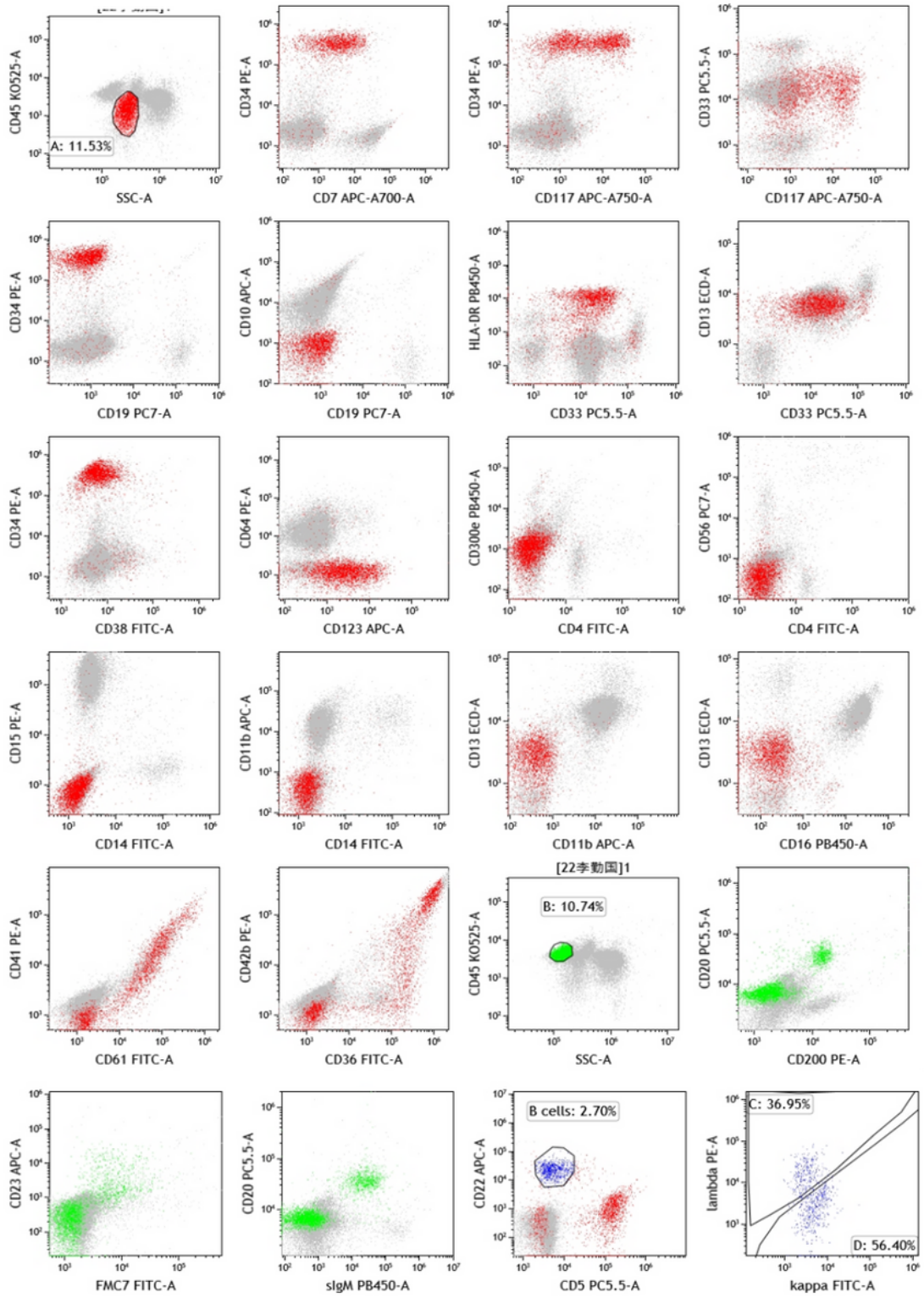

Figure 4

Karyotype showed 45, XY, del(5)(q21q34),-7[4]/46,sl,del(3)(q25),+mar[1]/46,sdl,del(2)(p21)[2]/46,XY[3].

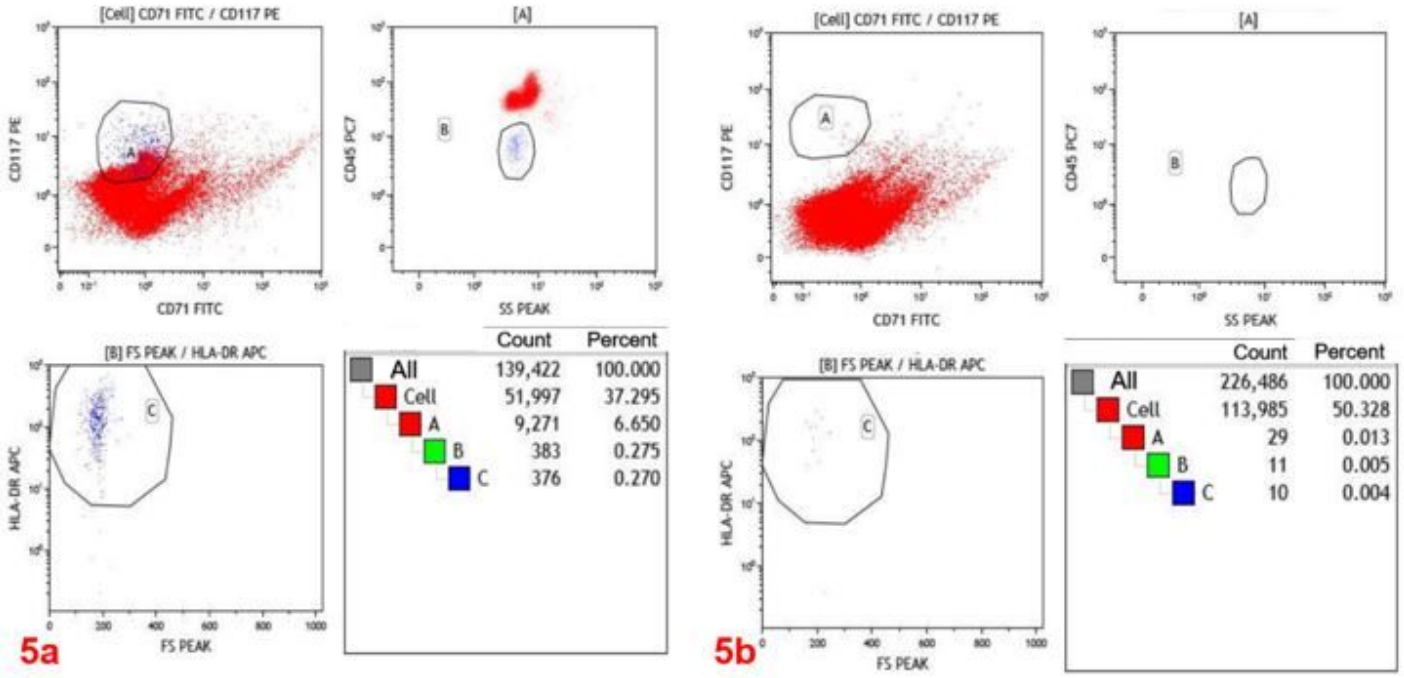

Figure 5

5a It was detected by flow detection before the second chemotherapy cycle that minimalresidualdisease (MRD) accounted for 0.723% of the total number (376/51997). 5b After the second chemotherapy cycle, MRD<0.01%.