Mixed Phenotype Acute Leukemia With Pml-rarα Positive: A Case Report and Literature Review

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Case Report

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Abstract

Mixed phenotype acute leukemia (MPAL) is an uncommon type of leukemia. It is one kind of malignant clonal diseases that expresses more than one genealogical specific antigen simultaneously. Most MPAL patients are associated with clonal chromosomal abnormalities and molecular genetic changes, such as t(9;22) (q34;q11) and KMT2A (MLL) rearrangement. These specific abnormalities usually have important guiding significance in MPAL diagnosis, targeted therapy and prognosis judgment. In this paper, we reported a case of MPAL, T/myeloid (M5) with an unfrequent combination of PML-RARα positivity and t(15;17). The treatment was successful with chemotherapy for both AML and ALL with daunorubicin, cytarabine (DA) and vincristine, prednisone (VP). We reported here this suggestive MPAL case of rare disease condition and effective treatment, in order to provide experience for the early diagnosis and treatment of similar patients.

Introduction

With the development of cytogenetics and molecular biology, researchers have gradually strengthened their understanding of acute leukemia (AL). Morphology, immunology, cytogenetics, and molecular biology (MICM) are widely used in the world, which is not only of great significance to study the pathogenesis and biological characteristics of leukemia, but also of practical value to guide clinical treatment and prognosis judgment. According to its basic immunophenotype, AL is usually classified as acute myeloid leukemia (AML), acute B lymphoid leukemia (B-ALL), and acute T lymphoid leukemia (T-ALL). However, there is a type of ambiguous lineage,which we call mixed phenotype acute leukemia (MPAL). MPAL is an extremely rare type, accounting for about 2–5% of all AL.(1, 2) It is characterized by the detection of at least two of three expression markers in myeloid lineage, B lineage and T lineage.

The current diagnosis of MPAL is mostly based on the relevant standards revised by World Health Organization (WHO) in 2016. Based on the updated WHO classification of hematological malignancies, MPAL can be divided into several subtypes including MPAL with t(9;22)(q34.1;q11.2); BCR-ABL1, MPAL with t(v;11q23.3); KMT2A rearranged, MPAL, B/myeloid, not otherwise specified (NOS) and MPAL, T/myeloid, NOS. (3)MPAL is one of highly heterogeneous malignancies, and the clonal origin of MPAL cells is still unclear. It may be derived from early hematopoietic stem cells and differentiate into myeloid and lymphoid leukemia cells during the development of AL. There is at present no unified treatment for this special type of leukemia. It is controversial on whether MPAL should be treated with a single chemotherapy or combined with chemotherapy for both lymphoid and myeloid leukemia, and whether bone marrow or peripheral blood stem cell transplantation is required. Thankfully, cell and molecular genetic abnormalities such as chromosomal translocations and gene mutations can be detected in most MPAL patients, which are of great significance for guiding the treatment and prognosis of MPAL patients. (2, 4)

Here we reported an extremely rare case of MPAL, T/AML(M5) with PML-RARα rearrangement and t(15;17). We discussed his diagnosis, treatment process and outcome in detail, and combined with

literature review, in order to provide experience for the early diagnosis and treatment of similar patients.

Case Report

A 35-year-old man was admitted to the Department of Hematology, The First Affiliated Hospital, College of Medicine, Zhejiang University, in May 2020, with bleeding gums of 3-day duration. Physical examination showed scattered petechiae throughout the body. Routine laboratory tests revealed severe thrombocytopenia (platelets $8*10^9$/L), abnormal white blood cell counts ($6.43*10^9$/L; 12.3% lymphocytes, 5.21% monocytes) and mild anemia (hemoglobin 100 g/L). Coagulation studies showed the international standardized ratio (INR) increased (1.18) and fibrinogen decreased (1.58), the others including thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (APTT) were normal. D-Dimer was raised to 11200. Lactate dehydrogenase (LDH) was slightly up to 385 U/L.

Morphology

A bone marrow aspirate showed monocyte proliferation was significantly active, with 72% of primitive monocytes + immature monocytes and 14% of mature monocytes, while other lines was inhibited. Moreover, Cytochemical staining suggested that myeloperoxidase (MPO), sudan black B stain (SB), nonspecific esterase (NSE) and NaF inhibit test were all positive. Based on bone marrow appearance, it was considered as acute nonlymphoblastic leukemia, morphologically resembling AML-M5b (Fig. 1).

Immunology

Immunophenotype with flow cytometry analysis found the protocell population accounted for about 79% of non-erythroid cells, expressing CD117, CD34, CD33, CD13, CD19 (weak), CD7, CD123, CD14, CD4, CD2, CD1a, MPO, cyCD3, and CD56 (sectional), which suggested the possibility of mixed T/ myeloid leukemia (Fig. 2).

Cytogenetics and molecular biology

Chromosomal analysis with G-banded karyotype of bone marrow cells showed 46, XY, t(15;17)(q24;q21)[9]/46, XY[9] (Fig. 3). Fluorescence in situ hybridization (FISH) confirmed that PML/RARα was positive. The positive rate of PML/RARα short form was 39%, while that of long form was negative. There was evidence of FLT3-ITD mutation and no evidence of IDH1, IDH2, CEBPA, c-kit or NPM1 mutations.

Clinical course

Based on his various auxiliary examinations, the diagnosis of MPAL was established. Then he was treated with daunorubicin, cytarabine (DA) and vincristine, prednisone (VP)(daunorubicin 120 mg Day 1–3 + cytarabine 100 mg Day 1–5; vincristine 4 mg Day 1, 8, 15 + prednisone 10 mg Day 1–21). The corresponding symptomatic support treatment also benefited the patient. The patient was subsequently treated with all-trans retinoic acid (ATRA) for maintenance therapy. There was no fever or bleeding during

the whole treatment. After one course of chemotherapy, the patient's complete blood count (CBC) returned to be normal. Bone marrow examination revealed a primordial granulocyte ratio of less than 5%. Thanks to the timely diagnosis of the disease and effective treatment regimens, the patient finally achieved complete remission (CR). At present, the patient has remained first CR during the over 3 months.

Discussion

MPAL has no specific chromosomal abnormalities. Owaidah et al. demonstrate that 68% of MPAL patients have clonal abnormalities, among which KMT2A translocation is the most common, followed by BCR-ABL.(5) KMT2A rearrangement is more frequent in pediatric MPAL (especially infants), while BCR-ABL is more frequent in adults.(6) The case described herein is interesting because PML-RARαrearrangement complicated with t(15;17) in MPAL cases is extremely uncommon. In general, PML-RARα fusion and t(15;17) are regarded as highly specific for acute promyelocytic leukemia (APL). There is few cases of AML with PML-RARα fusion and t(15;17) that were neither immunophenotypically nor morphologically consistent with APL.(7) To sum up, MPAL T/myeloid (M5) with PML-RARα positivity and t(15;17) is indeed quite rare.

MPAL is characterized by unique clinical and biological characteristics, with higher incidence in adults than in children, which is generally associated with worse prognosis.(4) There may be several reasons for the poor prognosis. First, the leukemia stem cells of MPAL are primitive pluripotent progenitors, which replicate too slowly to be resistant to chemotherapy. Second, due to the transformable phenotype, MPAL cells are capable to adapt to therapy. Third, a part of MPAL can highly express resistance-conferring P-glycoprotein.(8, 9) Therefore, the choice of chemotherapy regimen has always been a major difficulty in MPAL treatment. Gerr H, Rubnitz JE and their coworkers indicated that ALL-directed chemotherapy usually showed better outcome than AML-directed therapies. If the initial chemotherapy regimen was not effective, the conversion regimen could be chosen (from ALL-directed switch to AML-directed or vice versa). More than half of patients were able to achieve CR in the second regimen.(10, 11) Nevertheless, some researchers revealed that combined AML/ALL type regimens were more effective than single regimen. The CR rate of combined chemotherapy was the highest (71%), followed by ALL-directed (64%), and the lowest was AML-directed (33%).(12) As such, we managed the patient with combined chemotherapy for ALL and AML, which contributed to his achievement of CR.

In conclusion, we reported a pretty unfrequent case of MPAL with PML/RARα fusion and t(15;17). The outcome of this patient was markedly satisfactory with combined AML/ALL type regimens (DA + VP) and ATRA as well.

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.

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Authors' contributions

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

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Figures

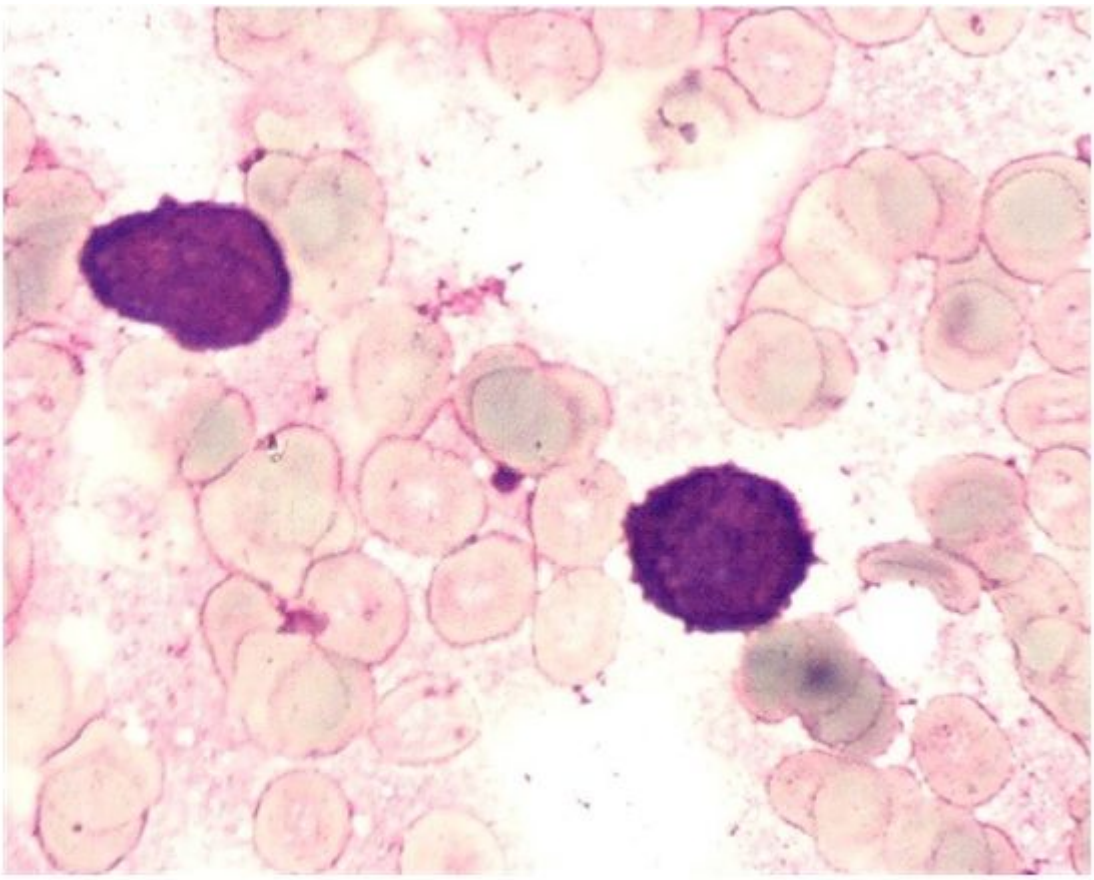

Figure 1. Bone marrow aspiration revealed morphological findings compatible with AML-M5b.

Figure 1

Bone marrow aspiration

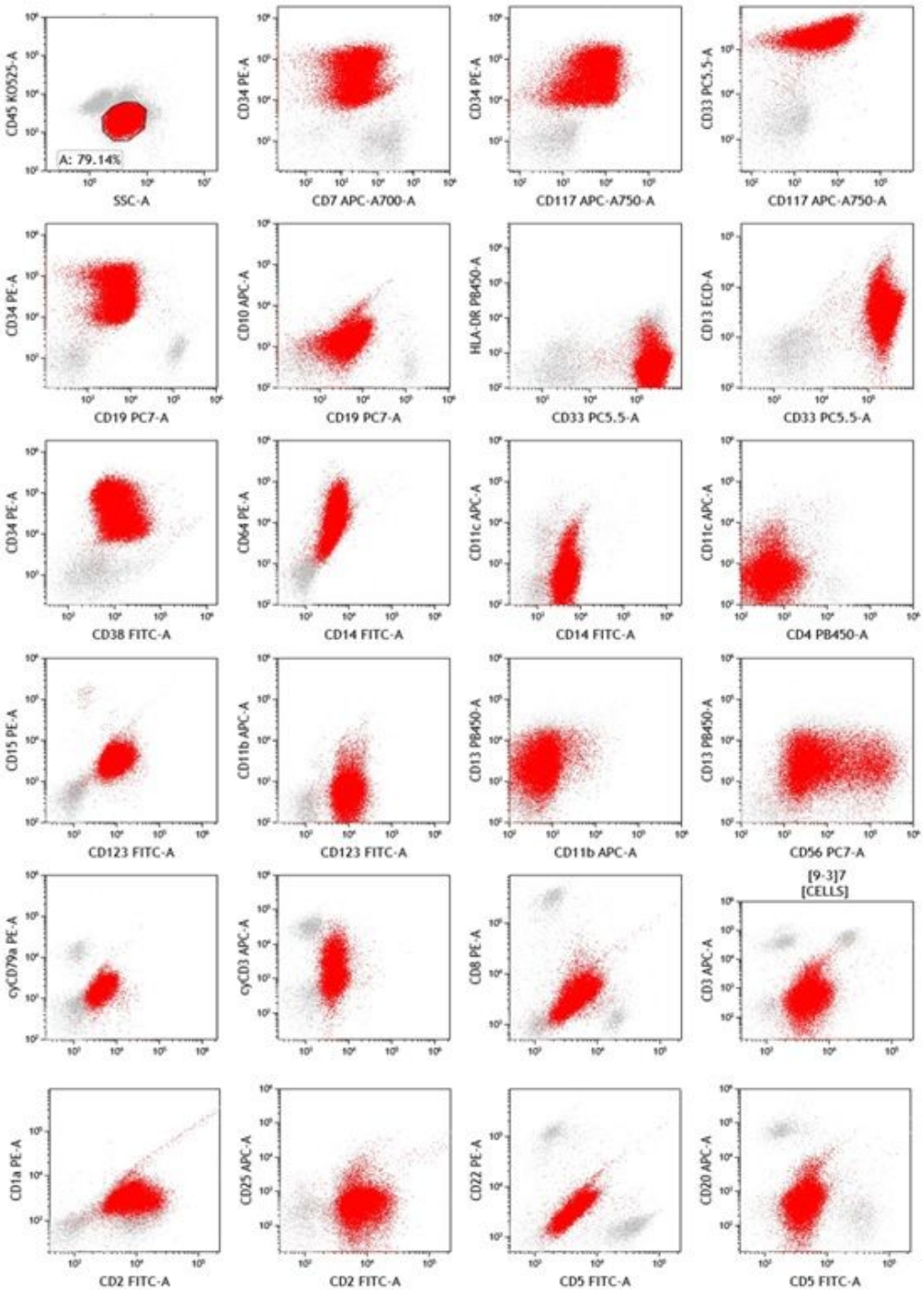

Figure 2. Immunophenotype with flow cytometry analysis suggested the possibility of mixed T/ myeloid leukemia.

Figure 2

Immunophenotype

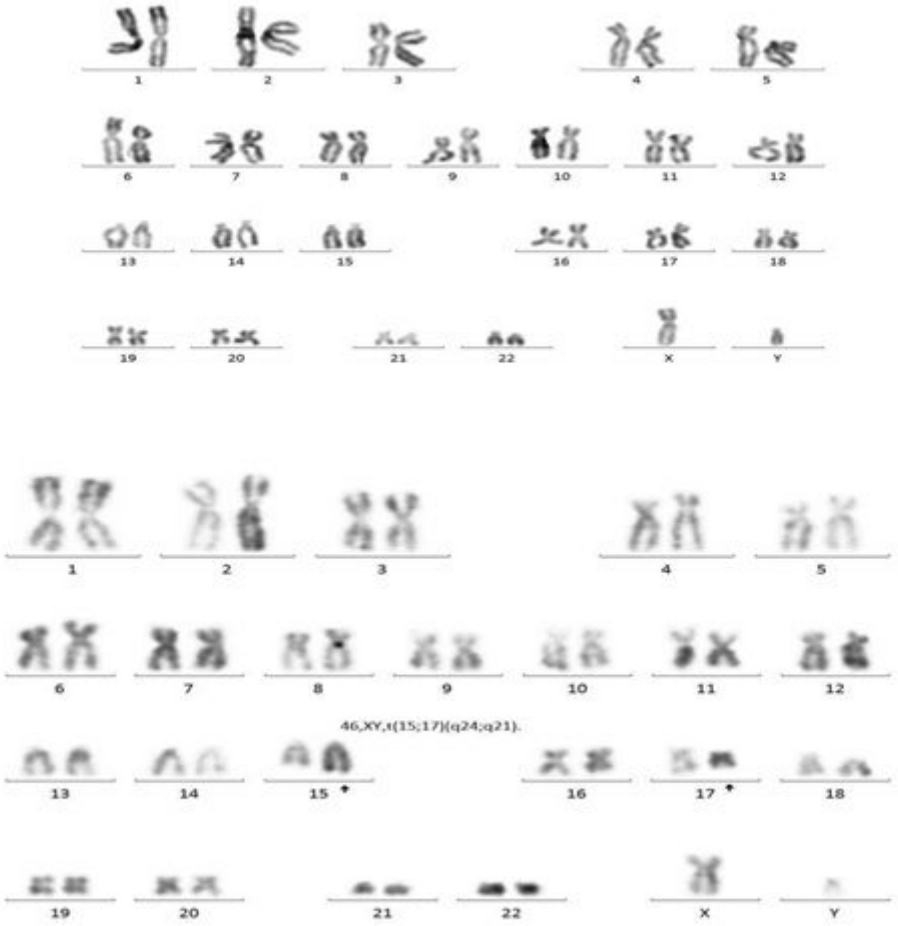

Figure 3. The karyotype is shown as 46,XY,t(15;17)(q24;q21)[3]/46,XY[9].

Figure 3

Karyotype