SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 19: 3587-3592, 2020

Imatinib therapy in acute myeloid leukemia with DEK-NUP214 and FIP1L1-PDGFRA rearrangement: A case report

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Received February 16, 2018; Accepted January 7, 2020

DOI: 10.3892/ol.2020.11455

Abstract. The fusion product of FIP1-like-1 (FIP1L1) and platelet-derived growth factor receptor α (PDGFRA) gene rearrangement is a tyrosine kinase oncoprotein sensitive to imatinib. This gene rearrangement characterizes a novel clinico-biological class of myeloid and lymphoid neoplasms with eosinophilia and PDGFRA abnormalities. The DEK proto-oncogene (DEK) and nucleoporin 214 (NUP214) rearrangement is rare in patients with acute myeloid leukemia (AML); therefore, the coexistence of DEK-NUP214 and FIP1L1-PDGFRA rearrangements in patients with AML is extremely rare. The present study presents a rare relapse case of a patient with AML with DEK-NUP214 and FIP1L1-PDGFRA rearrangements, without marked eosinophilia in the peripheral blood or bone marrow. Low-dose imatinib monotherapy without intensive chemotherapy was used to achieve complete hematological remission.

Introduction

In 2016, the World Health Organization defined myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet-derived growth factor receptor α (PDGFRA), platelet-derived growth factor receptor β (PDGFRB), fibroblast growth factor receptor 1 or pericentriolar material 1-janus kinase 2 (1,2). Although fusion genes are most frequently detected in patients with chronic clonal eosinophilic neoplasms, they are occasionally detected in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (3). In the presence of a ligand, FIP1-like-1 (FIP1L1)-PDGFRA fusion genes are constitutively active and encode novel chimeric kinases in a manner similar to that of breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL1) in chronic myeloid leukemia (CML) (4,5). Such activation results in hemopoiesis failure. Imatinib is a therapeutic inhibitor of tyrosine kinase enzymes, which is widely used in the treatment of patients with CML. The DEK proto-oncogene (DEK) and nucleoporin 214 (NUP214) rearrangement is indicated in 1% of patients with AML (6), and the coexistence of DEK-NUP214 and FIP1L1-PDGFRA rearrangements in patients with AML is extremely rare. The present study reports the case of a 23-year-old woman who was diagnosed with AML exhibiting both DEK-NUP214 and FIP1L1-PDGFRA rearrangements.

Case report

In December 2016, a 23-year-old woman presented with fever and fatigue that had persisted for 1 month. Treatment with antibiotics for 2 weeks resulted in no clinical improvement. Following admittance to the First Bethune Hospital of Jilin University (Changchun, China), the patient developed a more serious fever associated with anemia (hemoglobin, 27 g/l), thrombocytopenia ($8x10^9$ cells/l) and leukocytosis ($87x10^9$ cells/l). There were 56.0% myeloblasts in the peripheral blood smear, in which no marked eosinophilia existed. A bone marrow smear exhibited 46.0% myeloblasts, also without marked eosinophilia, featuring 36.5% granular blasts and 9.5% monoblasts associated with Auer corpuscle (Fig. 1). The immunophenotype of the blasts from the fresh bone marrow samples was identified using fluorescence-activated cell sorting (FACS) analysis. A population of 2.5% dysplastic myeloblasts expressed CD38, CD33 and $CD13^{dim}$, and did not express markers for myeloperoxidase and lymphocyte lineage.

A normal karyotype (20 metaphases with 46,XX) was identified in the bone marrow samples using a cytogenetic chromosome test. A normal karyotype without PDGFRA rearrangement was also identified by fluorescence *in situ* hybridization (FISH). Rearrangement in the FIP1L1-PDGFRA and the DEK-NUP214 fusion genes was identified using reverse transcriptase polymerase chain reaction (RT-PCR). Samples from the same individual were used to conduct RT-PCR and these data were analyzed using a paired t-test using GraphPad Prism (version 4; GraphPad Software, Inc.). $P<0.05$ was considered to indicate a statistically significant difference. The results for the other fusion

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Key words: acute myeloid leukemia, DEK proto-oncogene-nucleoporin 214 rearrangement, FIP1-like-1-platelet-derived growth factor receptor α rearrangement, imatinib, therapy

genes, FIP1L1-PDGFRAβ and fibroblast growth factor receptor 1 were negative. The relative expression of the FIP1L1-PDGFRA fusion gene was significantly decreased compared with the normal control PDGFRA gene (1.01±0.13 vs. 0.51±0.15; P=0.03; Fig. 2A). The relative expression of the DEK-NUP214 fusion gene was not significantly decreased compared with the normal control NUP214 gene (1.03±0.16 vs. 0.61±0.13; P=0.08; Fig. 2B). DNA sequencing analysis (7) mapping revealed that the exon 9 sequence of DEK was fused to the exon 18 sequence of NUP214 at the location indicated in Fig. 3A, and the exon 13 sequence of FIP1L1 was fused to the exon 12 sequence of PDGFRA at the location indicated in Fig. 3B. A conclusive diagnosis of AML associated with DEK-NUP214 and FIP1L1-PDGFRA rearrangements was thus made.

The patient was initially treated with 60 mg/m^2/d daunorubicin (days 1-3) and 100 mg/m^2/d cytarabine (days 1-7) by intravenous transfusion between January 13, 2017 and January 20, 2017. At the end of the treatment, the white blood cell count indicated a marked response, decreasing to 0.42x10^9 cells/l. A total of 14 days following induction chemotherapy, the bone marrow smear exhibited 12.5% myeloblasts and the immunophenotype exhibited 1.97% myeloblasts. A total of 32 days following induction chemotherapy, the bone marrow smear exhibited 58.5% myeloblasts. The patient was then treated with a second course of induction chemotherapy involving 10 mg/m^2/d idarubicin (days 1-3) and 100 mg/m^2/d cytarabine (days 1-7) by intravenous transfusion between February 20, 2017 and February 27, 2017. A total of 14 days following chemotherapy, 1.5% myeloblasts were detected, as demonstrated by morphological analysis of the bone marrow, and 0.48% myeloid blasts, as demonstrated by FACS analysis. For the first time, the patient achieved complete hematological remission. Between April 15, 2017 and April 21, 2017, the patient received 2 g/m^2/d cytarabine (every 12 h, days 1, 3 and 5) by intravenous transfusion. The patient maintained complete hematological remission following the third course of chemotherapy; however, therapy was discontinued due to personal reasons.

The patient refused intensive chemotherapy at the time of leukemia relapse on July 8, 2017. The patient consented to treatment with imatinib (Glivec), which is a first generation tyrosine kinase inhibitor. From July 12, 2017, the patient was treated with 200 mg imatinib oral administration once daily. After 30 days of targeted treatment with imatinib, 5% myeloblasts were detected in the bone marrow smear, which demonstrated effective control of leukemia progression. The patient maintained complete hematological remission with the same dose of imatinib for 2 months, but remained positive for both DEK-NUP214 and FIP1L1-PDGFRA rearrangements. On October 23, 2017, the leukemia relapsed and 47% myeloblasts were detected in the bone marrow smear. The patient received a re-induction chemotherapy regimen (10 mg/m^2/d cytarabine, days 1-14; 14 mg/m^2/d aclarubicin, days 1-4; and 5 μg/m^2/d recombinant human granulocyte-colony stimulating factor, days 1-14). After 14 days of chemotherapy, 38% myeloblasts were identified in the bone marrow smear indicating that the patient was not in remission. The patient left hospital without further intensive chemotherapy or hematopoietic stem cell transplantation.

Materials and methods

Antibodies and flow cytometry. Single cell suspensions of bone marrow were prepared using the standard techniques. Fresh peripheral bone marrow was layered onto Ficoll (cat. no. 171440-02; GE Healthcare) and centrifuged at 400 x g for 10 min at room temperature. Antibodies purchased from BD Biosciences included: Mouse anti-human CD38-FITC (cat. no. 340909), mouse anti-human CD117-PE (cat. no. 652806), mouse anti-human CD45-percp (cat. no. 652803), mouse anti-human CD34-APC (cat. no. 652837), mouse anti-human CD19-APC (cat. no. 652804), mouse anti-human CD16-FITC (cat. no. 555406), mouse anti-human MPO-FITC (cat. no. 652821), mouse anti-human CD4-FITC (cat. no. 340133), mouse anti-human CD33-PE (cat. no. 347787), mouse anti-human CD56-PE (cat. no. 652825), mouse anti-human CD3-APC (cat. no. 662525) and CD13-PE (cat. no. 652820). The isotype control mouse IgG2a (cat. no. 551414) was obtained from BD Biosciences. Dead cells were excluded by propidium iodine (PI) staining, while PI negative live cells were gated in for analysis. A 100 μl cell suspension (1x10^7/ml) was incubated with antibodies (1:1,000) for 15 min at room temperature. This was followed by 3 washes with PBS buffer and centrifugation at 1,500 x g for 10 min at room temperature following each wash. Data acquisition was performed with the FACS Calibur flow cytometer (BD Biosciences) using CellQuest software (BD Biosciences). Data analysis was performed using FlowJo software v.7.6.1 (Tree Star, Inc.).

Fluorescence in situ hybridization (FISH). Single cell suspensions of bone marrow were prepared using the standard techniques. Vysis 4q12 Tri-Color Rearrangement FISH Probe Kit (cat. no. 05N52-020; Abbott Pharmaceutical) was used according to the manufacturer's protocols. The spectrumGreen probe spans ~703 kb (chr4:53159272-53862621) and is located centromeric to the FIP1L1 gene region. The spectrumOrange probe spans ~448 kb (chr4:54045936-54494304) and is located between the FIP1L1 and the CHIC2 gene regions. The SpectrumAqua probe spans ~578 kb (chr4:54840090-55418505) and extends from the telomeric end of the PDGFRA gene region to beyond the KIT gene region. Interphase cells at a density of 1x10^6/ml were used. For each target area, 7 μl LSI/WCP Hybridization buffer, 1 μl probe and 2 U/l purified water were mixed in a microcentrifuge tube at ambient temperature and centrifuged at 1,500 x g for 1-3 sec. The tubes were vortexed and centrifuged again. Following this, the tubes were placed in a 73˚C water bath for 5 min and then on a 45-50˚C slide warmer until ready to apply probe to target DNA. To hybridize the probe to the DNA the slides were taken out of 100% EtOH and dried using a blotter and paper towel. Subsequently, the slides were placed on a 45-50˚C slide warmer for up to 2 min to evaporate the remaining EtOH. Probe mixture (10 μl) was applied to 1 target area and immediately covered with a coverslip. The process was repeated for additional target areas. The coverslip was sealed with rubber cement and the slides placed in a pre-warmed humidified box in a 37˚C incubator for 6-16 h. To produce an assay with sufficient signal, 12-16 h hybridization should be used for most LSI probes. As the samples were paraffin-embedded they were washed with 0.4*SSC/0.3% NP-40 wash solution. The slides

were air-dryed in the dark. DAPI II counterstain (10 μl) was applied to the target area of slide. The slides were visualised using a suitable filter combination on an optimally performing fluorescence microscope Olympus BX63 (Olympus Corp.).

RT-qPCR. Total RNA was isolated from bone marrow cells using the RNAqueous™ Total RNA Isolation kit (cat. no. AM1912; Thermo Fisher Scientific, Inc.), followed by reverse transcription using the High-Capacity cDNA Reverse Transcription kit (cat. no. 4368814; Applied Biosystems Inc.) according to the manufacturer's protocols. In brief, samples were incubated at 42˚C for 15 min followed by 95˚C for 3 min. qPCR was performed using the SYBR® Green master mix (cat. no. 4334973; Applied Biosystems Inc.) on a QuantStudio™ 6 Flex Real-Time PCR system (Applied Biosystems Inc.). The primers for human FIP1L1-PDGFRA (PDGFRA-R1: 5'-TGA GAGCTTGTTTTTCACTGGA-3'; PDGFRA-R2: 5'-GGG ACCGGCTTAATCCATAG; FIP1L1-F1: 5'-ACCTGGTGC TGATCTTTCTGAT-3'; FIP1L1-F2: 5'-AAAGAGGATACG AATGGGACTTG-3'). The primers for human DEK-NUP214 (R1: 5'-TCTCCCTGTTGGTTGATG-3'; F1: 5'-CCTACAGAT GAAGAGTTAA-'; R2: 5'-GTGTCTCTCGCTCTGG-3'; F2: 5'-GGCCAGTGCTAACTTGG-3'). A total of 26 thermo-cycling cycles were performed as follows: 95˚C for 5 min; 40 cycles of 95˚C for 30 sec, 58˚C for 30 sec and 72˚C for 60 sec. Gene expression was normalized to an internal control, GAPDH: forward, 5'-CCGGAATTCCGTTATGGGGAA GGTGAAG-3' and reverse, 5'-CGCGGATCCGTTTAAACT CAATGGTGATG-3'. The relative mRNA expression level of each gene was determined using the as $2^{-\Delta\Delta Cq}$ method (3).

Giemsa and hydrogen peroxide staining procedures. Blood smears ~50-100 μm thickness had 0.3% 4-8 drops of benzidine alcohol added to them drop-wise for 1 min. After 1 min, 4-8 drops of hydrogen peroxide were added immediately. When the slides turned blue they were washed immediately with water. Giemsa solution was diluted and used to stain the blood smears. The blood smears were fixed with formalin for 2-3 min at room temperature prior to staining. The blood smear should be thin and suitable and uniformly distributed. Giemsa was dropped to cover the blood smears at room temperature for 15-30 min. The slides were inspected using a fluorescent microscope OLYMPUS BX53 (Olympus Corp.) after drying.

Discussion

Although FIP1L1-PDGFRA rearrangement usually presents in patients with diseases such as chronic myeloproliferative neoplasms with eosinophilia, it also presents in patients with blastic phase chronic myeloproliferative neoplasms. In certain cases, FIP1L1-PDGFRA rearrangement is involved in AML or T-cell lymphoblastic lymphoma associated with marked eosinophilia (8,9). The present study reported the rare case of a young woman who was diagnosed with AML associated with DEK-NUP214 and FIP1L1-PDGFRA rearrangements. When the patient relapsed with leukemia, she achieved complete hematological remission within 1 month of imatinib monotherapy. The patient maintained complete hematological remission for 2 months. Therefore, imatinib monotherapy may effectively achieve complete hematological remission of this type of AML. Although remission lasted for only 2 months, this may provide enough time for the patient to prepare for

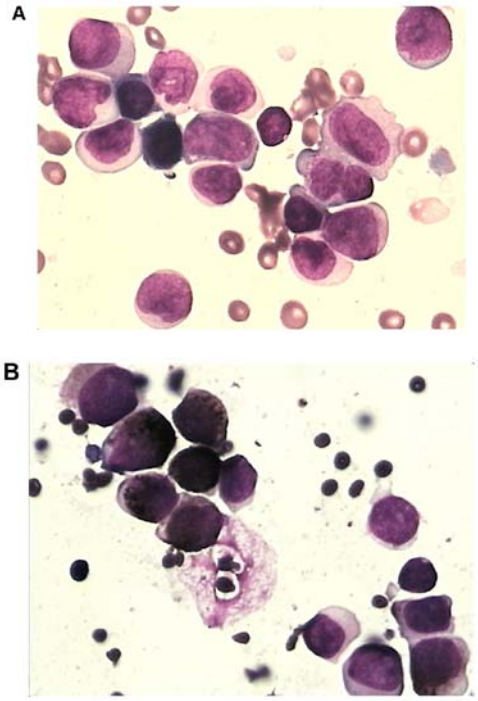

Figure 1. Bone marrow smears taken from the patient with AML. (A) Giemsa staining of a bone marrow smear taken at diagnosis of AML showing infiltration of granular blasts and monoblasts associated with Auer corpuscles. There was no increase in the levels of eosinophils (magnification, x1,000). (B) Peroxidase staining of a bone marrow smear exhibiting 47% strong positive, 20% weak positive and 33% negative staining (magnification, x1,000). AML, acute myeloid leukemia.

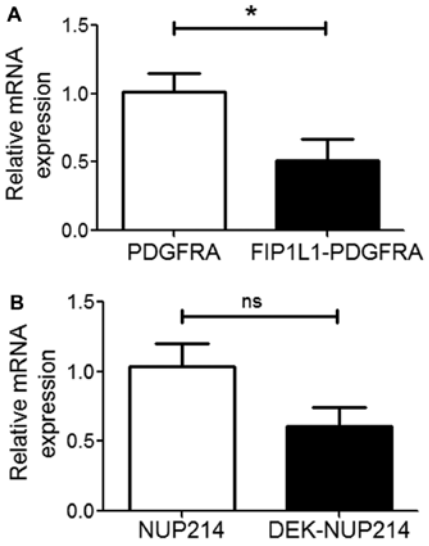

Figure 2. Relative expression levels of (A) FIP1L1-PDGFRA fusion gene compared with the normal control PDGFRA gene, which was significantly decreased (P=0.03) and (B) DEK-NUP214 fusion gene compared with the normal control NUP214 gene, which was not significantly decreased (P=0.08). n=5 samples from the patient per group. Significance was determined using a paired Student's t-test. Values indicate mean ± standard deviation. *P<0.05. DEK, DEK proto-oncogene; FIP1L1, FIP-like-1; ns, not significant; NUP214, nucleoporon 214; PDGFRA, platelet-derived growth factor receptor α.

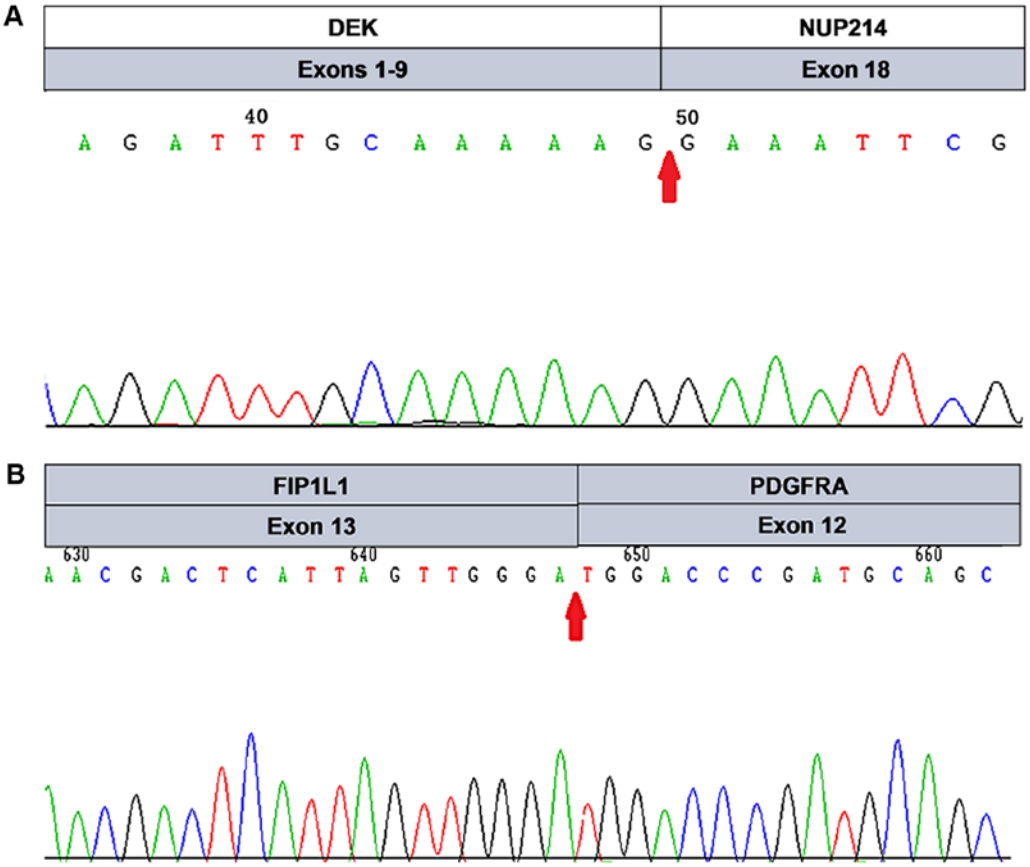

Figure 3. Partial FIP1L1-PDGFRA fusion gene sequence. (A) DEK exon 9 sequence fused to NUP214 exon 18 sequence at the indicated location (red arrow). (B) FIP1L1 exon 13 sequence fused to PDGFRA exon 12 sequence at the indicated location (red arrow). FIP1L1, FIP-like-1; PDGFRA, platelet-derived growth factor receptor α; DEK, DEK proto-oncogene; NUP214, nucleoporin 214.

hematopoietic stem cell transplantation. In the present case, there was no marked eosinophilia in the peripheral blood or bone marrow smears. Notably, the patient tested negative for FIP1L1-PDGFRA rearrangement when using FISH, but tested positive when using RT-PCR and sequencing analysis, which is due to the difference in sensitivity and detection between the methods.

AML blasts, as myeloid precursor cells with impaired differentiation, possess the characteristic of uncontrolled proliferation. A number of fusion gene rearrangements and gene mutations determine the prognosis of patients with this disease. It has been reported that patients with AML with a DEK-NUP214 rearrangement can present as patients with *de novo* AML with any morphological subtype of AML (10). The DEK-NUP214 rearrangement is commonly identified in young adults or patients with childhood AML. The prognosis of patients with AML with DEK-NUP214 is poor, and is similar to that of patients with AML with unfavorable cytogenetic abnormalities. Patients with this type of leukemia are treated with intense chemotherapy and hematopoietic stem cell transplantation, in order to achieve hematological or molecular remission. The presence of DEK-NUP214 rearrangement in patients with AML is associated with a poor response to standard chemotherapy and an increased rate of post-remission relapse (11). Hematopoietic stem cell transplantation has been indicated to improve the prognosis of patients with AML with DEK-NUP214 rearrangement compared with patients with AML with DEK-NUP214 rearrangement that received chemotherapy only (12,13).

Numerous studies have revealed that imatinib administration achieves complete hematological remission in patients diagnosed with AML, myeloid sarcoma, and B and T cell leukemia/lymphoma associated with FIP1L1-PDGFRA arrangement (2,3,14). FIP1L1-PDGFRA fusion results in constitutive activation of tyrosine kinase enzymes by disrupting the autoinhibitory juxtamembrane domain of PDGFRA (8). Administration of imatinib without chemotherapy is currently considered a standard therapeutic regimen for patients with chronic myeloproliferative neoplasms with FIP1L1-PDGFRA rearrangement (2). A previous study evaluated the therapeutic effects of imatinib on patients with chronic eosinophilic leukemia and the FIP1L1-PDGFRA fusion gene or a disease and the BCR-ABL1 fusion gene; the results revealed that patients with the FIP1L1-PDGFRA fusion gene are more sensitive to imatinib treatment than those with the BCR-ABL1 fusion gene (15). Therefore, to achieve hematological, cytogenetic or molecular remission, lower doses of imatinib (100-200 mg/d) without discontinuity were administered to patients with the FIP1L1-PDGFRA rearrangement in this previous study. By contrast, continuous imatinib administration (400-600 mg/d) was required for patients with BCR-ABL1 rearrangement (16). A recent study described a novel PDGFRB rearrangement, TBL1X receptor 1-PDGFRB, in a patient with AML with

DEK-NUP214. The patient presented with an aggressive form of AML, relapsing twice following allogeneic stem cell transplantation; however, treatment with dasatinib (the second generation of tyrosine kinase inhibitors followed by imatinib; 100 mg once daily) concurrently with chemotherapy plus irradiation resulted in control of the disease for 30 months and resolution of eosinophilia, indicating that this fusion gene may be sensitive to dasatinib (17).

Two previous studies, Barraco *et al* (2) and Valent *et al* (12) describe cases that are consistent with the present study. In one of these studies, the patient received imatinib (100 mg/d), and achieved morphological and molecular remission within 6 months of the first administration, which lasted for 36 months (2). Barraco *et al* (2) reported a patient with acute eosinophilia leukemia associated with FIP1L1-PDGFRA rearrangement. The patient was treated with imatinib monotherapy and achieved complete hematological, cytogenetic and molecular remission within 1, 3 and 6 months, respectively. Furthermore, the remission response without relapse lasted for 5 years. In the present case report, monotherapy with imatinib resulted in complete morphological remission within 1 month of leukemia relapse. However, monotherapy with imatinib did not achieve cytogenetic or molecular responses, and the leukemia relapsed after 2 months. The DEK-NUP214 rearrangement, as a factor of poor prognosis in patients with AML, may have affected the molecular responses and prognosis in this case.

The FIP1L1-PDGFRA fusion gene is a powerful clonality marker for the direct diagnosis of eosinophilia-associated disease (18), which is generated from a submicroscopic 800 kb interstitial deletion on chromosome 4, del(4)(q12q12). It has been reported that the interstitial deletion cannot be detected by conventional cytogenetic analysis or FISH, as the deleted segment contains the basic gene structure required for FISH testing (18). As a result, the majority of patients who present with eosinophilia possess a normal karyotype (1). Therefore, a diagnosis of eosinophilia relies on FISH analysis to detect the del(4)(q12q12), as well as RT-PCR to test for the FIP1L1-PDGFRA fusion gene (18,19). Furthermore, false-negative results can occur in FISH or RT-PCR testing. To improve the diagnostic accuracy, these two tools should be used together.

In conclusion, the present study reported that monotherapy with imatinib induced hematological remission even in a rare case of AML associated with DEK-NUP214 and FIP1L1-PDGFRA rearrangements when leukemia relapsed. During hematological remission, the patient was in good compliance with imatinib without side effects. The present case study indicated that the tyrosine kinase inhibitor may be a sensitive and effective treatment for patients with AML with FIP1L1-PDGFRA rearrangement. However, for this type of AML associated with two types of fusion genes, particularly the DEK-NUP214 fusion gene with poor prognosis, it is difficult to eradicate minimal residual leukemia in order to acquire long-term survival using chemotherapy or molecular-targeted monotherapy. It is necessary to treat this type of AML with hematopoietic stem cell transplantation in order to improve survival time. Furthermore, the combination of FISH and RT-PCR testing should be used for accurate diagnosis of patients with eosinophilia.

Acknowledgements

The authors would like to thank Dr Jing Bai Department of Hematology, First Bethune Hospital of Jilin University (Jilin, China) for their technical support.

Funding

The present study was funded by the Norman Bethune Program of Jilin University (grant no. 2012224) and the National Natural Science Foundation of China (grant nos. 81770149 and 81100350).

Availability of data and materials

The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

YT was the chief physician who provided the case and was a major contributor in writing the manuscript. YY provided funding and was a major contributor in writing the manuscript and performing the analysis and interpretation of data. HL performed the FISH. ZD performed the immunohistochemistry. RH performed the flow cytometry experiments. TY and JS performed the FISH and analyzed data. ZD analyzed the data. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient's father for publication of the present study; the patient authorized her father to provided informed consent as she was in ill health at the time.

Competing interests

The authors declare that they have no competing interests.

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