

CASE REPORT

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Transformation into acute myeloid leukemia with t(8;21)(q22;q22.1); *RUNX1::RUNX1T1* from *JAK2*-mutated essential thrombocythemia: a case report

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Abstract

Background Blast transformation is a rare but well-recognized event in Philadelphia-negative myeloproliferative neoplasms associated with a poor prognosis. Secondary acute myeloid leukemias evolving from myeloproliferative neoplasms are characterized by a unique set of cytogenetic and molecular features distinct from de novo disease. t(8;21)(q22;q22.1); *RUNX1::RUNX1T1*, one of the most frequent cytogenetic abnormalities in de novo acute myeloid leukemia, is rarely observed in post-myeloproliferative neoplasm acute myeloid leukemia. Here we report a case of secondary acute myeloid leukemia with t(8;21) evolving from *JAK2*-mutated essential thrombocythemia.

Case presentation The patient was a 74-year-old Japanese woman who was referred because of thrombocytosis (platelets $1046 \times 10^9/L$). Bone marrow was hypercellular with increase of megakaryocytes. Chromosomal analysis presented normal karyotype and genetic test revealed *JAK2* V617F mutation. She was diagnosed with essential thrombocythemia. Thrombocytosis had been well controlled by oral administration of hydroxyurea; 2 years after the initial diagnosis with ET, she presented with leukocytosis (white blood cells $14.0 \times 10^9/L$ with 82% of blasts), anemia (hemoglobin 91 g/L), and thrombocytopenia (platelets $24 \times 10^9/L$). Bone marrow was hypercellular and filled with 80% of myeloperoxidase-positive blasts bearing Auer rods. Chromosomal analysis revealed t(8;21)(q22;q22.1) and flow cytometry presented positivity of CD 13, 19, 34, and 56. Molecular analysis showed the coexistence of *RUNX1::RUNX1T1* chimeric transcript and heterozygous *JAK2* V617F mutation in leukemic blasts. She was diagnosed with secondary acute myeloid leukemia with t(8;21)(q22;q22.1); *RUNX1::RUNX1T1* evolving from essential thrombocythemia. She was treated with combination chemotherapy with venetoclax and azacitidine. After the first cycle of the therapy, blasts disappeared from peripheral blood and decreased to 1.4% in bone marrow. After the chemotherapy, *RUNX1::RUNX1T1* chimeric transcript disappeared, whereas mutation of *JAK2* V617F was still present in peripheral leukocytes.

Conclusions To our best knowledge, the present case is the first one with *JAK2* mutation preceding the acquisition of t(8;21). Our result suggests that t(8;21); *RUNX1::RUNX1T1* can be generated as a late event in the progression of *JAK2*-mutated myeloproliferative neoplasms. The case presented typical morphological and immunophenotypic features associated with t(8;21) acute myeloid leukemia.

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Keywords Myeloproliferative neoplasms, Essential thrombocythemia, Secondary acute myeloid leukemia, *JAK2* V617F, t(8;21)(q22;q22.1), *RUNX1::RUNX1T1*

Background

Philadelphia (Ph)-negative myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders characterized by the proliferation of mature blood cells. Among them, polycythemia vera and essential thrombocythemia (ET) are the most frequent entities associated with chronic and indolent clinical course. Activating mutations of the JAK/STAT signal pathway, primarily *JAK2*, *MPL*, and *CALR*, are present in the great majority of patients, exerting as primary pathogenesis leading to the proliferation of mature blood cells [1].

Blast transformation is a rare but well-recognized event in Ph-negative MPNs, associated with a grim prognosis. Secondary acute myeloid leukemias (AMLs) evolving from MPNs are characterized by a unique set of cytogenetic and molecular features distinct from de novo AML [2–5]. Somatic mutations in *TP53*, *ASXL1*, *IDH1/2*, *TET2*, and *RUNX1* genes were reported to occur frequently in post-MPN AML, comparing with those in de novo disease [3–5]. On the contrary, structural alterations of chromosomes such as t(8;21)(q22;q22.1), inv(16)(p13.1q22)/t(16;16)(p13.1;q22), and t(15;17)(q22;q11-12), known as the most common cytogenetic aberrations in de novo AML, are quite rare in post-MPN AML [6–16]. Here we report a case of t(8;21) AML evolved from *JAK2*-mutated ET.

Case presentation

A 72-year-old Japanese female patient was referred to the hospital because of thrombocytosis. She had no significant medical history. Peripheral blood showed hemoglobin 132 g/L, platelets $1046 \times 10^9/L$, and white blood cells $8.4 \times 10^9/L$. Bone marrow was hypercellular with increase of megakaryocytes (Fig. 1) and without increase of blasts (0.4%). Chromosomal analysis of bone marrow cells presented normal karyotype, and genetic tests revealed the presence of *JAK2* V617F mutation. She was diagnosed with ET. Thrombocytosis had been well controlled by the administration of hydroxyurea; 2 years after initial diagnosis, her routine blood examination showed leukocytosis (white blood cells $14.0 \times 10^9/L$ with 82% of blasts), anemia (hemoglobin 91 g/L), and thrombocytopenia (platelets $24 \times 10^9/L$). Bone marrow was hypercellular and infiltrated with 80% blasts, some of which possessed Auer rods (Fig. 2A). These blasts were positive for myeloperoxidase staining (Fig. 2B) and presented positivity for CD13, CD19, CD34, and CD56 on flow cytometry. G-banded chromosome analysis of

bone marrow cells showed 46,XX,t(8;21)(q22;q22.1)[4]/45,idem,-X[16]. *RUNX1::RUNX1T1* chimeric transcript was confirmed by reverse transcriptase polymerase chain reaction analysis. *BCR::ABL1* fusion was not detected. She was diagnosed with AML with t(8;21)(q22;q22.1); *RUNX1::RUNX1T1*.

Allogeneic hematopoietic transplantation therapy was discussed, but she was considered to be transplant-ineligible because of higher age. Single usage of JAK inhibitor (ruxolitinib) was also clinically impractical as its efficacy in this setting was not established. As hypomethylating agent therapy was increasingly recognized as an alternative to induction chemotherapy for post-MPN AML [5, 17], she was treated with combination chemotherapy by venetoclax and azacytidine. After the first cycle of the therapy, blasts disappeared from peripheral blood and decreased to 1.4% in bone marrow. During the course of the second cycle, she developed sepsis and pneumonia accompanying severe cardiac and respiratory failure. After the recovery from infections, she chose to be treated with best supportive care and the chemotherapy was discontinued.

For clonality analysis, RNA was prepared from CD34-sorted circulating leukemic blasts before chemotherapy and peripheral leukocytes after chemotherapy (65 days after the start of the therapy), consisting of 97% neutrophils, and subjected to reverse transcriptase polymerase chain reaction and nucleotide sequence analysis. As shown in Fig. 3, *RUNX1::RUNX1T1* chimeric transcript disappeared after chemotherapy, whereas

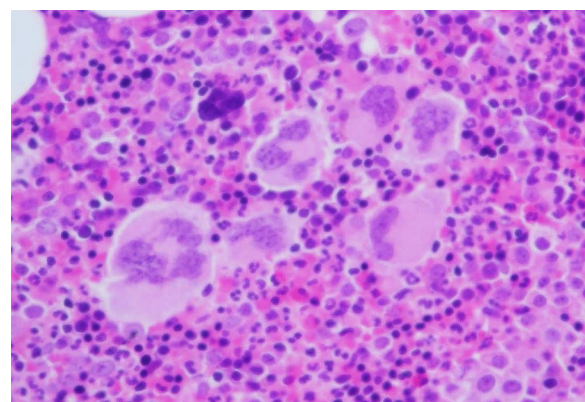


Fig. 1 Histopathology of bone marrow at the time of diagnosis with ET (hematoxylin and eosin, original magnification $\times 100$), showing hypercellular marrow with increase of large to giant megakaryocytes. Megakaryocytes presented increased cytoplasm and hyperlobulated nuclei

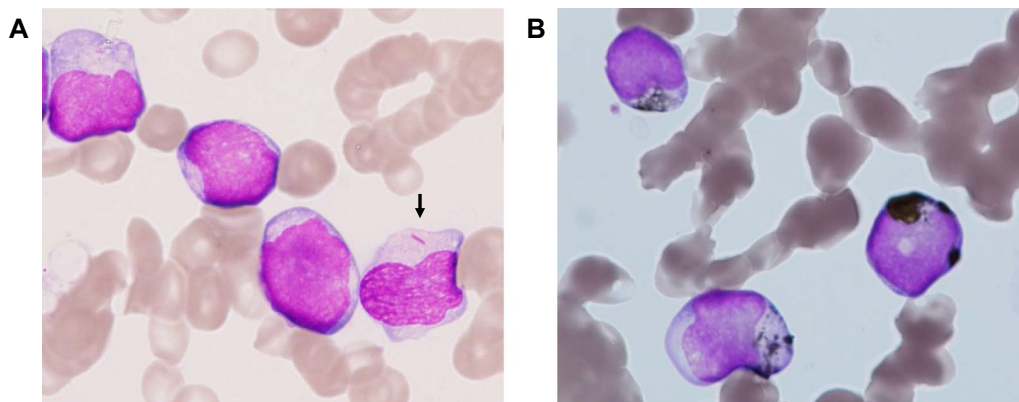


Fig. 2 **A** Morphologic features of blasts in bone marrow at the leukemic transformation (May-Giemsa staining, original magnification $\times 1000$). Blasts contained fine azurophilic granules in abundant basophilic cytoplasm; arrow shows a blast with a single and sharp Auer rod. **B** Blasts were positive for myeloperoxidase staining

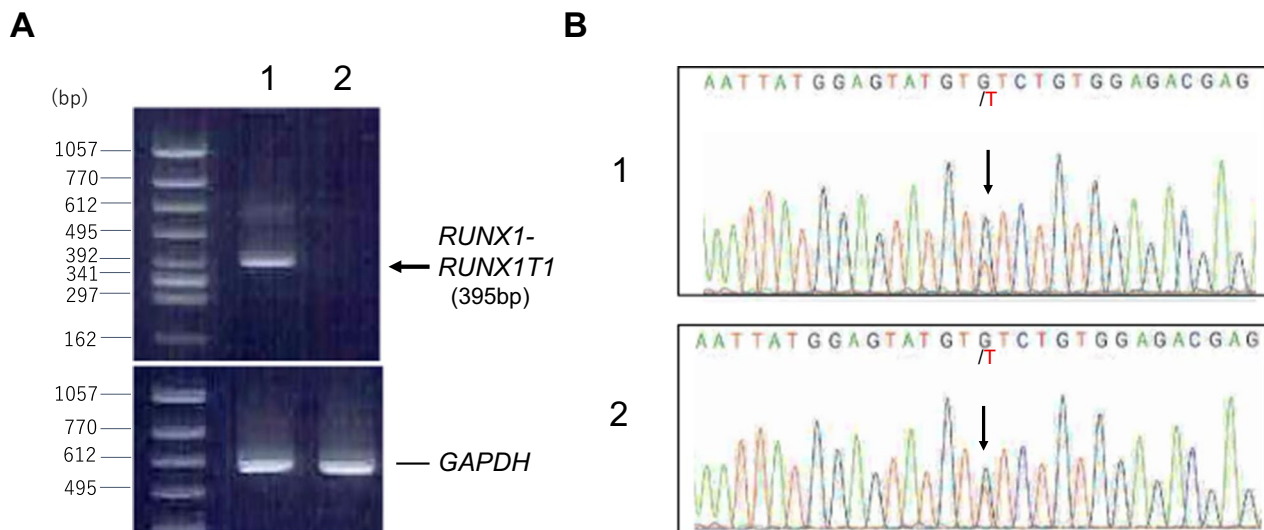


Fig. 3 **A** RT-PCR detecting *RUNX1::RUNX1T1* chimeric transcript. The sequences of primers were as follows; *RUNX1* (forward), 5'-CTACCGCAGCCATGAAGAACC-3'; *RUNX1T1* (reverse), 5'-AGAGGAAGGCCATTGCTGAA-3'. Lane 1; leukemic blasts before chemotherapy, lane 2; peripheral leukocytes after chemotherapy. **B** Sequence analysis showing *JAK2* V617F mutation. cDNA was amplified using primers, 5'-ATTTTAAAGGCGTACGAAGAGAAGTAG-3' (forward) and 5'-ATAAGCAGAATATTTTTGGCACATACAT-3' (reverse). PCR product containing the reported mutation point was directly sequenced. Arrows indicate G>T substitution. 1; leukemic blasts before chemotherapy, 2; peripheral leukocytes after chemotherapy

heterozygous mutation of *JAK2* V617F was present in both samples, indicating that the leukemic blasts were derived from *JAK2*-mutated ET clone. Mutation of *KIT* or *FLT-3* was not detected in leukemic blasts.

Discussion and conclusion

Recent studies revealed that secondary AMLs evolving from Ph-negative MPNs present unique cytogenetic and molecular features distinct from de novo AML, including the higher frequency of somatic mutations in *TP53*, *ASXL1*, *IDH1/2*, *TET2*, *EZH2*, and *RUNX1* genes and the lower frequency of those in *FLT3*, *MPM1*, *CEBPA*, and

WT1 [3, 4]. Chromosomal alterations related to poor-risk outcomes in MPNs include complex karyotypes, *inv(3)(q21.3q26.2)/t(3;3)(q21.3;q26.2)*, *i(17)(q10)*, *-7/7q-*, *12p-/12p11.2*, or *11q23* rearrangements [5].

On the contrary, balanced chromosomal translocations frequently observed in de novo AML with good-risk complex are quite rare in post-MPN AML; 11 cases of acute promyelocytic leukemia with *t(15;17)(q22;q11-12)*; *PML::RARA* evolved from MPNs were reported so far [6–15]. However, chromosomal rearrangements involving core binding factor genes, *t(8;21)(q22;q22.1)*; *RUNX1::RUNX1T1* or *inv(16)(p13.1q22)/t(16;16)*

(p13.1;q22); *CBFB::MYH11* were not reported, except for one case with ET-derived AML presenting t(8;21), in whom other gene mutations was not investigated [16]. Thus, to our best knowledge, the present case is the first one with *JAK2* mutation preceding the acquisition of t(8;21).

Coexistence of *JAK2* V617F mutation and t(8;21) chromosomal translocation is a rare but recurrent combination of genetic aberration in AML. *JAK2* mutation has been reported to occur in a small number of de novo AML, with a relatively high incidence in subtype with t(8;21) associated with unfavorable clinical outcomes [18–20]. In these cases, *JAK2* mutation was recognized as an additional genetic event after the formation of *RUNX1::RUNX1T1* chimeric gene. In our case, the opposite order of events, *JAK2* mutation preceding the acquisition of t(8;21) was postulated, indicating that the occurrence of t(8;21) can be a late event in the progression of MPN, similarly as in a few cases with chronic myeloid leukemia with occurrent t(8;21) translocation and Ph chromosome [21–26].

Although high frequency of erythroblastic and megakaryoblastic phenotype was reported in post-MPN AML [27], our case presented typical morphological and immunophenotypic features associated with t(8;21) AML, such as the emergence of Auer rod and the expression of CD19, CD34, and CD56 [28]. The findings indicated that late-appearing cytogenetic abnormality would also define the phenotype of secondary AML from MPN.

Hydroxyurea, the most common cytoreductive agent employed in the management of MPN, interferes with DNA synthesis and may have mutagenic and leukemogenic potential. However, the recent study indicated that the use of hydroxyurea does not increase the risk of secondary malignancies, including AML and myelodysplastic syndrome [29]. Thus, it remains undetermined whether hydroxyurea promoted the formation of *RUNX1::RUNX1T1* chimeric gene leading to leukemic transformation or not in this case.

Abbreviations

| | |
|-----|-----------------------------|
| MPN | Myeloproliferative neoplasm |
| AML | Acute myeloid leukemia |
| ET | Essential thrombocythemia |
| Ph | Philadelphia |

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Author contributions

CA wrote the manuscript and took care of the patient. TS, KS, IO, AO, RA, and YI edited the manuscript and took care of the patient. EK performed molecular analysis. YM and YT reviewed and edited the manuscript. YN wrote and edited the manuscript. All authors approved the final manuscript and consented to publish the manuscript.

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Availability of data and materials

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

Declarations

Ethical approval and consent to participate

The study was performed with prior approval of the Institutional Review Board and the Ethics Committee of the Saitama Medical University Hospital (the committee's reference number: 12-089). Written informed consent for the study was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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