**MLL-PTD in a 13-year-old patient with blast phase myeloproliferative neoplasm**

A case report

Zhipeng He, MM, Bixin Wang, MM, Lili Chen, MM, Yiping Huang, MM, Huixian Wang, MM, Mengting Yang, MM, Xueting Xiao, MM, Yanhong Lu, MM, Jiaying Chen, MM, Yong Wu, MD*

---

**Abstract**

**Rationale:** The risk of leukemic transformation in myeloproliferative neoplasm (MPN) has been increasing with time. Partial Tandem Duplications of the MLL gene (MLL-PTD) has been reported in de novo acute myeloid leukemia (AML), but not in MPN blast phase. The post-MPN AML developed adverse clinical outcomes, which showed no noticeable improvement over the past 15 years. Therefore, the mechanisms and therapeutic approaches of post-MPN AML need to be deeply studied.

**Patient concerns:** In this study, we present a JAK2V617F positive MPN patient who experienced fatigue and splenomegaly, transforming into JAK2V617F negative AML.

**Diagnoses:** A diagnosis of acute monocytic leukemia was made in MPN blast phase.

**Interventions:** The patient received chemotherapy and allogeneic hematopoietic stem cell transplantation (Allo-SCT).

**Outcomes:** The patient achieved complete remission twice, but relapsed twice. Relapse-free survival was only 3 months. She died about 24 months after her diagnosis.

**Lessons:** MLL-PTD occurs in the progression of JAK2V617F positive MPN into JAK2V617F negative AML, which may be a novel mechanism of MPN blast phase and helpful for post-MPN AML diagnosis. Allo-SCT may be a good choice for post-MPN AML with MLL-PTD. More therapeutic strategies need to be explored for a better prognosis in these patients.

**Abbreviations:** Allo-SCT = allogeneic hematopoietic stem cell transplantation, AML = acute myeloid leukemia, ET = essential thrombocythemia, MLL-PTD = Partial Tandem Duplications of the MLL Gene, MPN = myeloproliferative neoplasms, PMF = primary myelofibrosis, PV = polycythemia vera.

**Keywords:** acute myeloid leukemia, MLL-PTD, myeloproliferative neoplasms

---

**1. Introduction**

Myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), are clonal disorders characterized by aberrant production of one or more terminally differentiated myeloid lineages. The discovery of JAK2V617F firstly revealed the molecular pathogenesis of MPN in 2005. The JAK2V617F mutation was detected in more than 95% of patients with PV, about 60% of patients with ET or PMF.[1] The risk of leukemic transformation in MPN varies among the MPN subtype and the frequency for acute myeloid leukemia (AML) deriving from MPN is highest in PMF, namely 10% to 20% at 10 years. The post-MPN AML developed adverse clinical outcomes, which showed no noticeable improvement over the past 15 years.[2] Therefore, the mechanisms and therapeutic approaches of post-MPN AML need to be deeply studied. Here, we reported a JAK2V617F positive PMF patient transformation into JAK2V617F negative AML with Partial Tandem Duplications of the MLL gene (MLL-PTD).

---

**2. Consent**

This study was approved by Ethical Committee of Union Hospital Affiliated to Fujian Medical University, and written informed consent was obtained from the patient’s parents.

---

**3. Case presentation**

A 13-year-old PMF patient with fatigue was admitted to Union Hospital Affiliated to Fujian Medical University in April 2016. Apart from the sign of splenomegaly, peripheral blood cell counts showed white blood cell (WBC) \(50.45 \times 10^9/L\), hemoglobin (Hb) 81 g/L, platelet (PLT) \(237 \times 10^9/L\), and 1% blast cell. Bone marrow showed granulocytic hyperplasia and
increased myelocytes. Bone marrow biopsy indicated myelofibrosis with reticulum fiber (+++). Chromosomal G-banding analysis revealed a normal 46, XX karyotype. JAK2V617F was detected, but no other molecular abnormality was found. No significant past medical history was got. Primary myelofibrosis was diagnosed according to the WHO criteria for PMF (2016). She was treated with hydroxyurea (0.5 g qd) and aspirin (100 mg qn). Ten months later, peripheral blood cell counts revealed WBC 3.02 × 10^9/L, Hb 62 g/L, PLT 224 × 10^9/L. Bone marrow showed acute mononcytic leukemia with 39.4% blasts cells. Bone marrow biopsy revealed acute myeloid leukemia, and myelofibrosis with reticulum fiber (+++). MPO (+) and CD15 (++) was detected by immunohistochemistry analysis. Interestingly, JAK2V617F mutation became negative. Meanwhile, MLL-PTD fusion gene and TET2 mutation were detected (Table 1). Acute monocytic leukemia (M5) was diagnosed according to the French-American-British (FAB) classification.

The patient received IA regimen (idarubicin 10 mg/m² × 3 days, and cytarabine 100 mg/m² × 7 days) for treatment induction. One month after the chemotherapy, bone marrow achieved complete remission. She received the IA regimen and high-dose cytarabine (2 g q12h × 3 days) for one-cycle consolidation therapy, respectively. Three months after initial chemotherapy, bone marrow showed relapse. Then, the FLAG regimen (fludarabine 38 mg d2–d6, cytarabine 1.5 g d2–d6, granulocyte colony stimulating factor 300 μg d1–d7) was adopted for reinduction. One month after the reinduction chemotherapy, bone marrow achieved no complete remission. Therefore, she received allogeneic hematopoietic stem cell transplantation (Allo-SCT) for salvage treatment. One month after the Allo-SCT, bone marrow displayed complete remission and MRD was negative. Three months after the Allo-SCT, the patient complained of abdominal pain, diarrhea and fever. MRD showed 6%, WT1 showed 64.1%, which indicated relapse of AML and acute graft versus host disease (aGVHD). She received a regimen of decitabine (2.5 mg d1–d5), aclacinomycin (20 mg d3–d5), homoharringtonine (4 mg d3–d5), and cytarabine (1 g d3–d5) for 2 cycles, with immunosuppressive therapy included. Eight months after the Allo-SCT, symptoms of acute rejection were within control. The blood cell counts showed WBC 1.29 × 10^9/L, Hb 63 g/L, PLT 22 × 10^9/L. Bone marrow aspiration showed a hypocellular marrow with 71.5% blasts. Nine months after the Allo-SCT, the patient died of infection.

4. Discussion

In this case, the JAK2V617F positive PMF transformed into JAK2V617F negative AML with MLL-PTD and TET2 mutation detected at 10 months after PMF diagnosis. We supposed that the emerging molecular abnormalities may be associated with secondary leukemia. It was previously reported that JAK2V617F positive MPN (9/17) transformed into JAK2V617F negative AML, which could be partly explained by a common clonal origin rather than mitotic recombination. The Ten-Eleven-Translocation (TET) family of proteins (TET1, TET2, and TET3) mainly lead to DNA demethylation by oxidizing mC to hydroxymethylcytosine (hmC). TET2 mutation might occur before or after JAK2V617F mutated MPN. The mutation order affected the clinical characteristics and response to JAK2 inhibitors in MPN. Besides, TET2 mutation could be acquired in post-MPN AML with positive or negative JAK2V617F, which cooperated with other somatic mutations leading to secondary AML. As in this patient, TET2 mutation occurred late during the leukemic transformation. Whereas, prognosis for TET2 mutation in post-MPN AML was controversial. The MLL gene, that encodes a transcription factor of histone H3 lysine 4 methyltransferase activity, is converted to MLL-PTD fusion gene through a gain-of-function intragenic self-fusion mutation. MLL-PTD that had not been detected in MPN, was reported in about 5% of patients with cytogenetically normal AML (CN-AML) and associated with poor prognosis. Sun et al reported that MLL-PTD, which occurred after TET2 mutation and acted in synergy with other mutations to contribute to leukemia, was a highly specific driver gene in AML. Additionally, the sequence of acquired gene mutation was of profound implication for targeted therapeutic strategies. This mechanism also accounts for the leukemic transformation in this PMF patient. The post-MPN AML was of adverse prognosis, with a median overall survival of 3.6 months. However, the treatment of Allo-SCT was superior to chemotherapy, with the complete remission rate 35% and 19%, respectively. The 3- and 5-year survival rates of patients received Allo-SCT were 32% and 10%, respectively. The patient in our study survived for about 24 months after her diagnosis. She achieved complete remission twice, but relapse-free survival was only 3 months. Allo-SCT may be a good choice for post-MPN AML with MLL-PTD. Also, more beneficial treatment strategies need to be explored for a better prognosis.

5. Conclusion

In conclusion, we report for the first time that MLL-PTD, cooperated with TET2 mutation, occurs during the progression of JAK2V617F positive PMF into JAK2V617F negative AML, which may be a novel mechanism of MPN blast phase and helpful for post-MPN AML diagnosis. The sequence of mutated gene in the evolution of AML is of great significance for targeted therapy. Perhaps, MLL-PTD targeted therapy combined with Allo-SCT will be a new direction for overcoming the post-MPN AML.

Author contributions

Conceptualization: Zhipeng He.
Data curation: Bixin Wang, Lili Chen.
Investigation: Yiping Huang, Huixian Wang, Mengting Yang, Jiaying Chen.
Writing – original draft: Zhipeng He.
Writing – review & editing: Zhipeng He, Bixin Wang, Xueting Xiao, Yanhong Lu, Yong Wu.

References

[1] Silvennoinen O, Hubbard SR. Molecular insights into regulation of JAK2 in myeloproliferative neoplasms. Blood 2015;125:3388–92.
[2] Tefferi A, Mudireddy M, Mannoni F, et al. Blast phase myeloproliferative neoplasm: Mayo-AGIMM study of 410 patients from two separate cohorts. Leukemia 2018;32:1200–10.
[3] Theocharides A, Boissinot M, Girodon F, et al. Leukemic blasts in transformed JAK2-V617F-positive myeloproliferative disorders are frequently negative for the JAK2-V617F mutation. Blood 2007;110:375–9.
[4] Tahiliani M, Koh KP, Shen Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science 2009;324:930–5.
[5] Ortmann CA, Kent DG, Nangalia J, et al. Effect of mutation order on myeloproliferative neoplasms. N Engl J Med 2015;372:601–12.
[6] Couronne L, Lippert E, Andrieux J, et al. Analyses of TET2 mutations in post-myeloproliferative neoplasm acute myeloid leukemias. Leukemia 2010;24:201–3.
[7] Damm F, Markus B, Thol F, et al. TET2 mutations in cytogenetically normal acute myeloid leukemias: clinical implications and evolutionary patterns. Genes Chromosomes Cancer 2014;53:824–32.
[8] Bernot KM, Siebenaler RF, Whitman SP, et al. Toward personalized therapy in AML: in vivo benefit of targeting aberrant epigenetics in MLL-PTD-associated AML. Leukemia 2013;27:2379–82.
[9] Racher U, Schnittger S, Kern W, et al. Distribution of cytogenetic abnormalities in myelodysplastic syndromes, Philadelphia negative myeloproliferative neoplasms, and the overlap MDS/MPN category. Ann Hematol 2009;88:1207–13.
[10] Dohner K, Tohis K, Ulrich R, et al. Prognostic significance of partial tandem duplications of the MLL gene in adult patients 16 to 60 years old with acute myeloid leukemia and normal cytogenetics: a study of the Acute Myeloid Leukemia Study Group Ulm. J Clin Oncol 2002;20:3254–61.
[11] Schnittger S, Kinkelin U, Schoch C, et al. Screening for MLL tandem duplication in 387 unselected patients with AML identify a prognostically unfavorable subset of AML. Leukemia 2000;14:796–804.
[12] Sun QY, Ding LW, Tan KT, et al. Ordering of mutations in acute myeloid leukemia with partial tandem duplication of MLL (MLL-PTD). Leukemia 2017;31:1–0.