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Short report

Acute myeloid leukemia with t(8;21)(q22;q22.1)/*RUNX1-RUNX1T1* and *KIT* Exon 8 mutation is associated with characteristic mastocytosis and dismal outcomes

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ABSTRACT

KIT mutations are observed in about 20–40% of acute myeloid leukemia with t(8;21)(q22;q22.1)/*RUNX1-RUNX1T1* [abbreviated AML t(8;21) here] with mutations involving exon 17 being the most common. Despite high frequencies of *KIT* mutations in both AML t(8;21) and systemic mastocytosis (SM), AML t(8;21) associated with SM is uncommon, and restricted to *KIT* exon 17 mutated cases. In this study, we report two cases of AML t(8;21) associated SM that *KIT* mutation occurred in exon 8 (T417_D419delinsY). In both patients, the bone marrow displayed increased round/ovoid mast cells with bilobated nuclei and absence of CD2 and CD25 expression. *RUNX1/RUNX1T1* fusion was shown in both myeloblasts and mast cells by FISH. Patient #1 was refractory to induction chemotherapy and died at day 50; patient #2 had residual AML, marked SM, and persistent *RUNX1/RUNX1T1* fusion after induction therapy.

1. Introduction

Acute myeloid leukemia (AML) with t(8;21)(q22;q22.1)/*RUNX1-RUNX1T1*(previously called *AML1-ETO*) often exhibits distinctive clinicopathologic features and is often associated with favorable outcome (Arber et al., 2017). The Runt domain of transcription factor *RUNX1* is essential for differentiation of hematopoietic stem cells, whereas the fusion protein RUNX1/RUNX1T1 acts as a transcriptional repressor and inhibits the expression of RUNX1 responsive genes, which in turn causes a block in hematopoietic stem cell differentiation(Asou, 2003). Studies have shown that *RUNX1-RUNX1T1* fusion, by itself, is incapable of leukemogenesis and additional genetic events are necessary for development of AML. Among these additional genetic changes, activating *KIT* mutations appear to be the most common, occurring in 20–40% of patients with AML with t(8;21)(q22;q22)/*RUNX1-RUNX1T1* [abbreviated here as AML t(8;21)](Wang et al., 2005; Care et al., 2003; Paschka et al., 2006; Schnittger et al., 2006).

KIT, located on chromosome 4q12, has 21 exons and encodes a type III receptor tyrosine kinase that contains an extracellular domain (ECD), a single hydrophobic transmembrane domain (TMD), and a protein tyrosine kinase (PTK) domain(Yang et al., 2010). KIT binds to stem cell factor or KIT ligand leading to dimerization of the protein and activation of downstream signaling pathways(Yang et al., 2010). *KIT* mutations occur in ~2% of AML of all types(Schnittger et al., 2006), but at a frequency of 20–40% in core binding factor AML, either AML t(8;21) or AML with inv(16)(p13q22) or t(16;16)(p13;q22)/*CBFB-MYH11* Wang et al., 2005; Care et al., 2003; Paschka et al., 2006; Schnittger et al., 2006, Cairoli et al., 2006; Gari et al., 1999, Qin et al., 2018). *KIT* mutations are often confined to either the ECD (exon 8) or PTK (exon 17, especially code D816) domains. *KIT* exon 8 mutations are detected predominantly in patients with AML with inv(16)/t(16;16) and rarely in patients with AML t(8;21); whereas exon 17 mutations are more commonly detected in AML t(8;21) and less commonly in AML with inv(16)/t(16;16)(Care et al., 2003; Paschka et al., 2006; Schnittger et al., 2006; Cairoli et al., 2006; Gari et al., 1999). Most mutations are point mutations that lead to hyperactivation of the receptor in response to stem cell factor (exon 8) or constitutive *KIT* activation (exon 17) (Wang et al., 2005; Kohl et al., 2005).

Systemic mastocytosis (SM) associated with a hematological neoplasm (SM-AHN) is diagnosed in up to 40% of all cases with SM and mostly are myeloid neoplasms. Despite a high frequency of *KIT* mutations, concurrent SM and AML t(8;21) is rare with less than 20 cases being reported(Johnson et al., 2013; Pullarkat et al., 2009; Pullarkat et al., 2007; Gadage et al., 2012; Cornet et al., 2012; Intzes et al., 2011;

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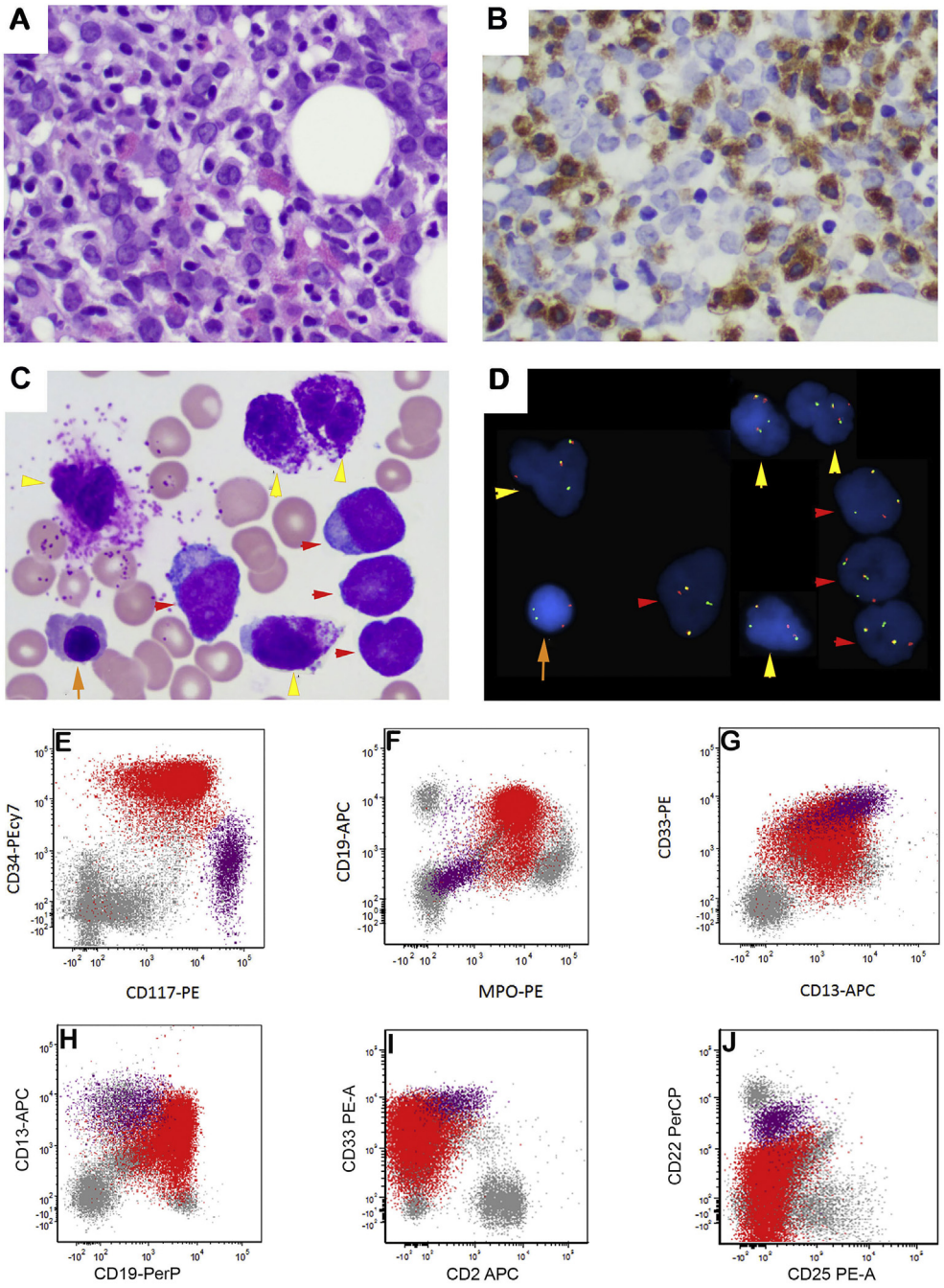

Fig. 1. Case #1. A: Bone marrow core biopsy shows increased immature cells and mast cells with abundant pale cytoplasm and bilobated nuclei (H&E, 400×). B: Mast cells are highlighted by tryptase (400×). C: Bone marrow aspirate smear shows increased blasts (red arrow head) and mast cells (yellow arrow head) (1000×). D: Map-back FISH analysis with *RUNX1/RUNX1T1* dual-color dual-fusion probe on the smear shown in Fig. 1C shows two fusion signals (yellow) presented in both blasts and mast cells, but not in erythroblast (orange arrow). *E*-J: Flow cytometric analysis show blasts (red) are positive for CD13, CD19, CD33, CD34, CD117 (partial), and MPO; mast cells (purple) are positive for CD13, CD22 (dim), CD33, CD117 (bright), and negative for CD2, CD19, CD25, CD34, and MPO. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Bernd et al., 2004; Nagai et al., 2007; Pullarkat et al., 2003; Wong et al., 1991). Among the patients who had concurrent SM and AML t(8;21) and who had *KIT* mutation tested, all showed point mutations on *KIT* D816 or N822(Johnson et al., 2013; Pullarkat et al., 2009; Cornet et al., 2012), and none showed *KIT* exon 8 mutation. In addition, the mast cells often showed spindle cell morphology and had aberrant expression of CD25 and/or CD2. Patients with concurrent SM and AML t(8;21) are often refractory to induction chemotherapy, have high relapse rate and poor outcomes(Johnson et al., 2013; Pullarkat et al., 2009).

Here we describe two patients who presented with AML t(8;21) and SM with *KIT* mutation involving exon 8. The mast cells showed round/ovoid shape with bilobated nuclei, and did not express CD2 or CD25. Neither patient achieved complete remission; patient #1 died 50 days after diagnosis and patient #2 had persistent disease at the last follow-up, suggesting that the coexisting SM with exon 8 *KIT* mutation identifies a poor prognostic subset of patients with AML t(8;21).

2. Case reports

2.1. Case #1

A 62-year-old woman presented with generalized weakness, shortness of breath, left upper quadrant discomfort, bone pain, easy bruising, and a 20-pound weight loss. A complete blood cell count (CBC) showed white blood cell (WBC) 4.8×10^9/L, hemoglobin 8.2 g/dL, platelets 11×10^9/L, and 62% circulating blasts. Computerized tomography (CT) scan showed splenomegaly and bilateral pulmonary nodules concerning for fungal infection. Bone marrow (BM) core biopsy showed hypercellular (90%) marrow with markedly increased immature cells admixed with mast cells, the latter was highlighted by immunostains for tryptase (Fig. 1A and 1B) and CD117. The mast cell infiltrate was interstitial, forming loose aggregates. The aspirate smears showed markedly increased blasts (61%) and mast cells (20%). The blasts were

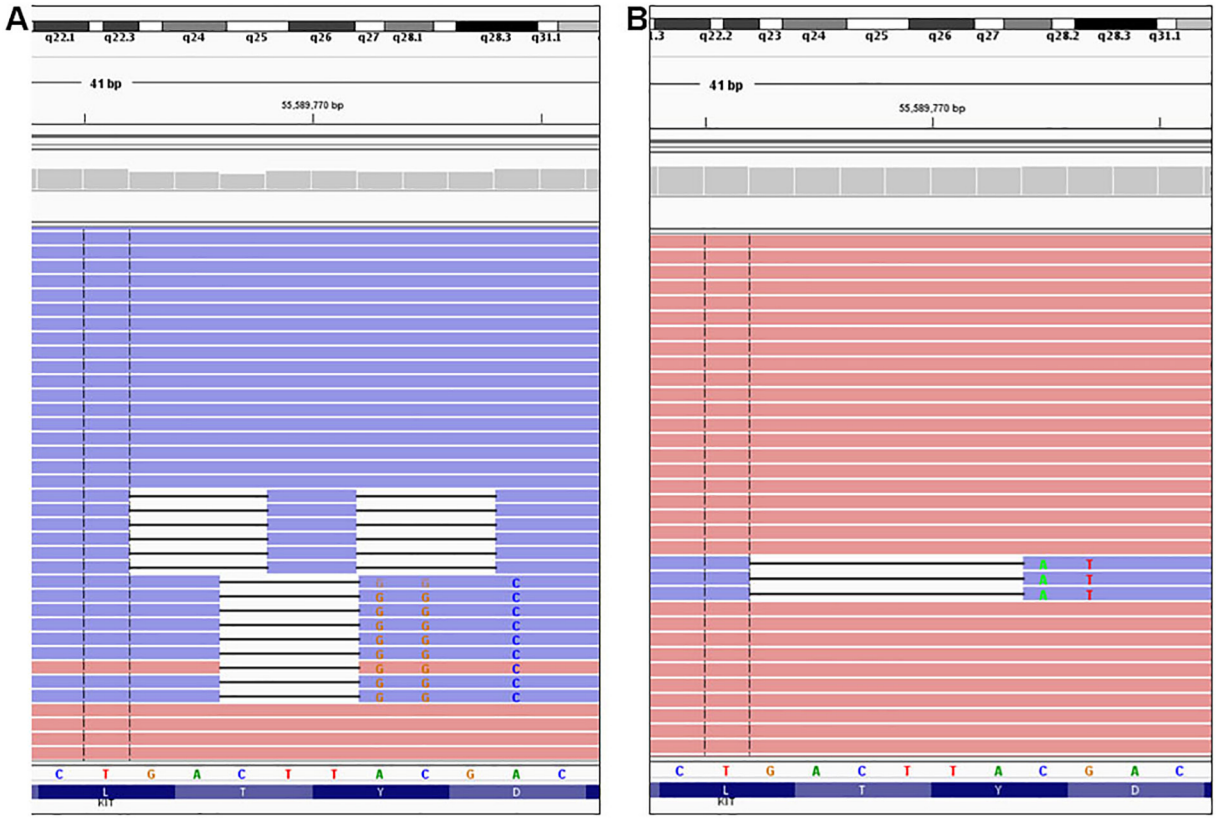

Fig. 2. Next generation sequencing analyses detected *KIT* mutation in exon 8 in both patients. A (Case #1): (top) NM_000222.2(*KIT*):c.1248_1255delinsTTp.T417_D419delinsY and (bottom) NM_000222.2(*KIT*):c.1250_1256delinsGGGCp.T417_D419delinsRA; B (Case #2): NM_000222.2(*KIT*):c.1248_1255delinsATp.T417_D419delinsY.

medium to large, some with distinct nucleoli, and only rare blasts had perinuclear hofs or Auer rods. Most of the mast cells were round/ovoid or slightly irregular, with bilobated nuclei and considerable amounts of metachromatic granules, some with degranulation. Occasional immature mast cells were seen, but spindle-shaped mast cells were not identified (Fig. 1C).

Chromosomal analysis revealed 46,XX,t(8;21)(q22;q22)[18]/46,XX[2]. Fluorescence *in situ* hybridization (FISH) analysis detected *RUNX1/RUNX1T1* fusion in 94% of cells, and map-back FISH analysis showed that the *RUNX1/RUNX1T1* fusion (yellow signals) was present in both blasts and mast cells (Fig. 1C and D). Flow cytometric immunophenotypic analysis revealed an aberrant myeloblast population (red, 60% of total events) positive for CD13, CD19, CD33, CD34, CD38, CD117, CD123, HLA-DR, MPO, and TdT (partial), and a mast cell population with an unremarkable immunophenotype (purple, 10% of total events) positive for CD13, CD22 (dim), CD33, CD117 (bright), and negative for CD2, CD19, CD25, and MPO (Fig. 1E-J). Next generation sequencing (NGS) using an 81-genes that are frequently mutated in hematopoietic neoplasms (Supplemental 1) detected two mutations in *KIT* Exon 8: NM_000222.2(KIT):c.1248_1255delinsTTp.T417_D419delinsY (Fig. 2A Top) and c.1250_1256delinsGGGCp.T417_D419delinsRA (Fig. 2A, bottom) with a variant allele frequency (VAF) of 26% and 10.5%, respectively. NGS also showed mutations on *ASXL1 and CBL*.

The patient was treated with fludarabine, cytarabine and granulocyte colony stimulating factor (G-CSF) plus idarubicin (FLAG-IDA) and gemtuzumab (anti-CD33 antibody). However, she failed to achieve remission. Her clinical course was complicated by epistaxis, hemoptysis, and respiratory distress. The patient died of multiorgan failure 50 days after initial diagnosis.

2.2. Case #2

A 57-year-old woman presented with dyspnea, dizziness, and recurrent falling. Laboratory tests at another hospital showed WBC 17.9×10^9/L, hemoglobin 3.0 g/dL, platelets 8×10^9/L, and 69% circulating blasts. BM biopsy showed 70% cellularity and 60% myeloblasts. Conventional cytogenetic analysis showed 46,XX,t(8;21)(q22;q22)[19]/46,XX[1] and FISH analysis confirmed *RUNX1/RUNX1T1* fusion (percentage unknown). Flow cytometry immunophenotyping detected an aberrant myeloblast population positive for CD13, CD19, CD33 (partial), CD45 (dim), CD64 (partial), CD117, HLA-DR, and MPO. There was no comment on mast cells. A diagnosis of AML t(8;21) was established and the patient received "7 + 3" induction chemotherapy (cytarabine 90 mg/m$^2\times$ 7 days, idarubicin 10.8 mg/m$^2\times$ 3 days). A follow-up BM at day 14 showed hypocellular (5%) BM with 1% blasts, but FISH showed persistent *RUNX1/RUNX1T1* fusion in 47% of cells. The patient was transferred to our institution at day 38 after diagnosis for a second opinion regarding consolidation therapy. Of note, the two BM biopsy specimens performed at the original hospital at time of initial diagnosis and on day 14 after therapy were not available for review at our institution.

A CBC at our institution (day 38) showed WBC 7.5×10^9/L, hemoglobin 9.7 g/dL, and platelet count 245×10^9/L; no blasts were seen in the blood smear. BM aspiration and biopsy showed 50% cellularity, 2% blasts, and 16% mast cells (Fig. 3A and B). Similar to patient #1, the mast cells were round/ovoid, many had bilobated nuclei, some of these cells showed degranulation (Fig. 3B). Mast cells were highlighted by immunostains for tryptase (Fig. 3C) and CD117 (Fig. 3D), but not CD2 (Fig. 3E) or CD25 (Fig. 3F). Flow cytometric immunophenotypic analysis detected a small number of abnormal myeloblasts (0.1% of total events) consistent with minimal residual AML, and a large number of mast cells (5.1% of total events). The mast cells had an unremarkable

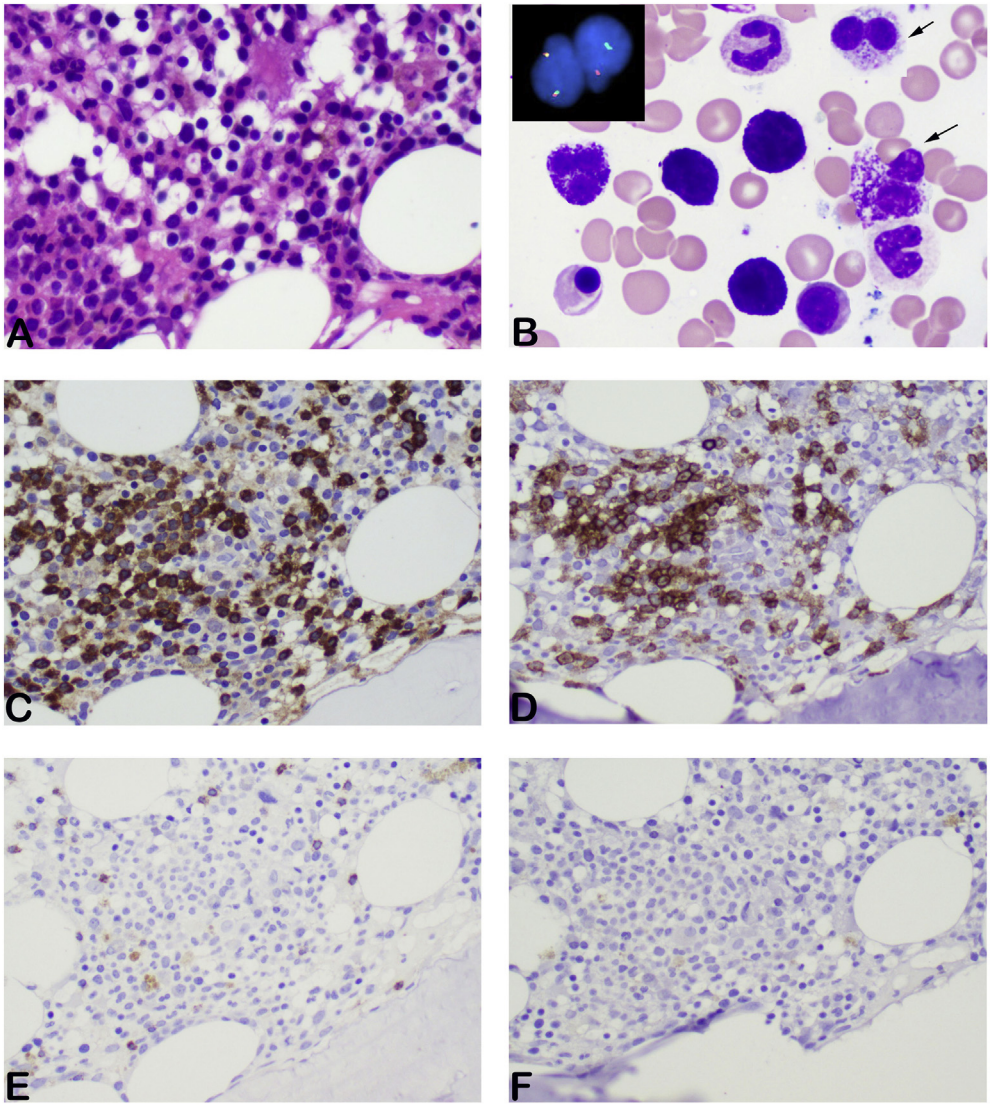

Fig. 3. Case #2. A. Bone marrow core biopsy shows increased mast cells with abundant pale cytoplasm (H&E, 400×). B: Bone marrow aspirate shows increased mast cells, some with degranulation (arrow, 1000×). An insertion on the left upper corner shows a bilobated nucleus (mast cell) which is positive for *RUNX1/RUNX1T1* rearrangement. C-F: immunohistochemistry stains on core biopsy show mast cells are positive for tryptase (C) and CD117 (D), but negative for CD2 (E) and CD25 (F).

immunophenotype, negative for CD2, CD25, and CD30. Conventional chromosomal analysis showed 46,XX[20]. FISH analysis detected *RUNX1/RUNX1T1* fusion in 10% of the cells; most were bilobated (mast cells, insertion in Fig. 3B right upper corner). NGS using an 81-gene panel showed a *KIT* mutation in exon 8: NM_000222.2(KIT):c.1248_1255delinsATp.T417_D419delinsY, with a VAF of 1.9% (Fig. 2B).

The patient was recommended to receive consolidation therapy using FLAG-IDA at the local hospital. At the last follow-up on day 80, the patient complained shortness of breath and chest pain and the CBC showed pancytopenia with no circulating blasts.

3. Discussion

We present these two cases because we believe they expand the spectrum of SM associated with AML t(8;21). Most cases with SM associated with a clonal, non-mast cell hematologic neoplasms reported in the literature have a *KIT* D816V mutation (exon 17), spindle mast cell morphology, and an abnormal mast cell immunophenotype. The two cases we present are unique, associated with an uncommon *KIT* mutation in exon 8 T417_D419delinsY; round/ovoid mast cells with bilobated nuclei; and negative for CD2 and CD25 expression. Both cases fulfilled at least one major (mast cell aggregates) and one minor (abnormal morphology) criteria for SM. Of note, the finding of frequent mast cells with bilobated or multilobated nuclei has been correlated with an aggressive mast cell proliferation.(Horny et al., 2017)

KIT mutations in AML occur primarily in a subset of core binding factor AMLs, including AML with t(8;21)/*RUNX1-RUNX1T1* and AML with inv(16)/t(16;16)/*CBFB-MYH11* [4, 8]. *KIT* mutations have been detected in 20–40% of AML with t(8;21)(Arber et al., 2017; Care et al., 2003; Paschka et al., 2006), usually exon 17 codon D816V. The roles of t(8;21)/*RUNX1T1/RUNX1* and *KIT* mutation in the pathogenesis of AML have been proposed by "two-hit" hypothesis: Class II mutations (including *RUNX1T1/RUNX1* fusion) often lead to impairment of differentiation and apoptosis of hematopoietic progenitors and Class I mutations (including *KIT* mutations) often confer a proliferative and survival advantage to hematopoietic progenitors. The collaboration of Class I and Class II mutations leads to fully developed AML(Wang et al., 2005; Becker et al., 2008). Among the cases with SM and AML t(8;21) that have been reported, the mutations were exclusively located in exon 17 at codons of D816 and N822 (Johnson et al., 2013; Pullarkat et al., 2009; Cornet et al., 2012). The two cases with SM and AML t(8;21) we

report here harbored *KIT* mutation in exon 8 (T417_D419delinsY). Mutation of T417_D419delinsY is uncommon and has been found in less than 5% of all AMLs and in 0.9% of patients with AML t(8;21) with *KIT* mutation (Gari et al., 1999; Qin et al., 2018; Kohl et al., 2005). It is not clear whether the reported single case of AML t(8;21) with *KIT* exon 8 T417_D419delinsY also had mastocytosis(Qin et al., 2018). The mutation of T417_D419delinsY results in a three amino acid deletion (417–419) and one amino acid (tyrosine) insertion on the extracellular domain of the KIT protein, which leads to hyperactivation of the receptor in response to stem cell factor(Yang et al., 2010; Gari et al., 1999; Kohl et al., 2005). ECD mutant-mediated *KIT* hyperactivation is *AKT* dependent, has different biological functions, and potentially is associated with more aggressive forms of SM than those associated with *KIT* D816V (Yang et al., 2010).

Mast cells are often increased in AML t(8;21). In one study of 40 cases of AML t(8;21) where mast cells were thoroughly worked-up, 4 (10%) patients met criteria for SM, 1 met criteria for myelomastocytic leukemia, and 8 had “mast cell hyperplasia”(Johnson et al., 2013). In another study which also included 40 cases of AML t(8;21), 5 (12.5%) patients had more than 10% of mast cells (2 with more than 20%) (Pullarkat et al., 2013) with normal morphology and lack of CD25 expression, but harbored *RUNX1/RUNX1T1* fusion. These studies suggest that the frequency of mastocytosis may have been underestimated in patients with AML t(8;21), due to an incomplete work-up. For example, none of our patients had serum tryptase performed, which is one of the minor criteria in the diagnosis of SM. Furthermore, at the time of initial diagnosis of AML t(8;21), the mast cell proliferation is likely masked by the extensive infiltration of myeloblasts in the BM (Johnson et al., 2013), and may only become evident after induction therapy when the AML is in morphological remission(Bernd et al., 2004). In addition, mast cells may be subtle and difficult to appreciate unless they are markedly increased and show a spindle shape. Due to abnormal morphology, mast cells could be mistaken as basophils. In the literature, most cases of AML t(8;21) with SM have spindle mast cells and aberrant CD25 expression (CD2 might not be tested). Our case #2 showed 1% of blasts, but 44% of cells had *RUNX1/RUNX1T1* fusion at day 14 BM, suggesting that most of the cells with *RUNX1/RUNX1T1* fusion were mast cells or maturing/matured myeloid cells.

In general, AML t(8;21) is associated with a favorable prognosis with a high remission rate, low relapse rate, and long survival. *KIT* mutations in AML t(8;21) often confer a worse prognosis(Care et al., 2003; Paschka et al., 2006; Cairoli et al., 2006), and patients with AML t(8;21) associated SM often have a dismal outcome. (Johnson et al., 2013; Pullarkat et al., 2009; Gadage et al., 2012; Cornet et al., 2012; Intzes et al., 2011; Bernd et al., 2004; Wong et al., 1991) Adding our two patients to the 18 cases reported in the literature, 9 patients failed induction chemotherapy; 9 achieved morphological remission of AML after induction but had persistent SM (and some rapid relapse); 1 achieved complete remission (CR), but relapsed with myeloid sarcoma one year later; and only 1 patient achieved CR with no history of relapsed leukemia(Johnson et al., 2013). This is in contrast to a favorable prognosis in AML t(8;21) as a group, which has approximately 90% CR (Byrd et al., 1999; Bloomfield et al., 1998). A few case reports showed that mast cells persisted and carried *RUNX1/RUNX1T1* fusion after the AML was in remission or even after hematopoietic stem cell transplant (Pullarkat et al., 2009). These findings suggest that mast cells are often resistant to AML-based chemotherapy and may serve as a “reservoir” for a leukemic clone, leading to disease relapse and a poor outcome. Currently, FLAG-IDA is widely used as a standard therapeutic protocol for patients with AML t(8;21) and is effective for most patients. However, this chemotherapy regimen may not be adequate for patients who have associated SM, and additional treatments with a tyrosine kinase inhibitor potentially may be effective in AML t(8;21) associated with SM and *KIT* mutation(Yang et al., 2010; Pullarkat et al., 2009).

In summary, AML t(8;21) associated with SM can rarely harbor *KIT* mutation in exon 8 (T417_D419delinsY). In such cases, mast cells often exhibit round/ovoid with bilobated nuclei and do not show aberrant expression of CD2 and CD25. Patients with these neoplasms often have an aggressive clinical course. Although further study on a larger cohort of patients is warranted, these two patients reported suggest that identification of *KIT* T417_D419delinsY mutation is important for appropriate risk stratification and management in patients with AML t(8;21).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yexmp.2019.04.009.

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