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ORIGINAL ARTICLE

Systemic mastocytosis associated with t(8;21)(q22;q22) acute myeloid leukemia

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Abstract Although *KIT* mutations are present in 20–25% of cases of t(8;21)(q22;q22) acute myeloid leukemia (AML), concurrent development of systemic mastocytosis (SM) is exceedingly rare. We examined the clinicopathologic features of SM associated with t(8;21)(q22;q22) AML in ten patients (six from our institutions and four from published literature) with t(8;21) AML and SM. In the majority of these cases, a definitive diagnosis of SM was made after chemotherapy, when the mast cell infiltrates were prominent. Deletion 9q was an additional cytogenetic abnormality in four cases. Four of the ten patients failed to achieve remission after standard chemotherapy and seven of the ten patients have died of AML. In the two patients who achieved durable remission after allogeneic hematopoietic stem cell transplant, recipient-derived neoplastic bone marrow mast cells persisted despite leukemic remission. SM associated with t(8;21) AML carries a dismal prognosis; therefore, detection of concurrent SM at diagnosis of t(8;21) AML has important prognostic implications.

Keywords Systemic mastocytosis · Acute myeloid leukemia · *KIT* mutations · Pathogenesis · Translocation (8;21) · Prognosis

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Introduction

The t(8;21)(q22;q22) occurs in about 5% of all acute myeloid leukemias (AML) and in 10% of cases of AML with FAB-M2 morphology [1]. The Runt domain transcription factor *RUNX1 (AML1)* is essential for differentiation of hematopoietic stem cells. The t(8;21) generates the *RUNX1-RUNX1T1 (AML1-ETO)* fusion protein that acts as transcriptional repressor and inhibits the expression of *AML1* responsive genes. This in turn causes a block in hematopoietic stem cell differentiation which in conjunction with additional genetic events leads to leukemic transformation [2, 3]. Studies have shown that t(8;21) by itself is incapable of leukemogenesis and additional genetic events are necessary for development of AML [4, 5]. Among these additional genetic changes that cooperate with *RUNX1-RUNX1T1* fusion to cause AML, activating *KIT* mutations appear to be the most common. Data suggest that activating

mutations in the receptor tyrosine kinases such as *KIT* play a role in the development of overt t(8;21)AML [5–8].

Systemic mastocytosis (SM) occurs due to an activating *KIT* mutation in a hematopoietic progenitor that leads to abnormal proliferation and accumulation of neoplastic mast cells in the bone marrow and other organs. In a subset of SM termed systemic mastocytosis with associated hematological non-mast cell disease (SM-AHNMD) in the current WHO classification, SM coexists with hematologic malignancies that are usually of myeloid origin [1, 9]. SM-AHNMD comprises 20% of all cases of SM and the most common associated hematologic malignancies are acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloproliferative disorders, and myelodysplastic/myeloproliferative syndromes such as chronic myelomonocytic leukemia [10–13].

In previous studies, the frequency of *KIT* mutations involving exon 17 as represented by a single amino acid substitution at D816 in patients with t(8;21)(q22;q22) AML have ranged from 12% to 24.2% [14–17]. Most common mutations described were at D816 and involved the Asp to Val substitution (D816V) [14–17]. Other substitutions included D816H, D816Y, and those at N822 including N822K and N822T [14–17]. Despite the fact that activating exon 17 *KIT* mutations are not uncommon in t(8;21) AML, a review of published literature suggests that SM associated with t(8;21) AML is exceedingly rare. Data on such cases are limited and largely confined to a handful of single case reports. We report our experience with SM associated with t(8;21)(q22;q22) AML and review the current literature on this rare entity.

Materials and methods

Patients with t(8;21) AML who also met WHO criteria for SM either at initial diagnosis or at relapse were identified from the databases of our institutions. Additional cases were identified by PubMed search of the English language literature as well as from the reference list of the reported cases [17–20]. Immunohistochemistry for CD117, tryptase, and CD25 staining was performed using standard techniques. Polymerase chain reaction (PCR) amplification and direct sequencing of the exon 17 of the *KIT* gene were performed by methods previously described [9]. Briefly, genomic DNA was isolated from bone marrow specimens using a QiAmp kit (Qiagen, Valencia, CA, USA). The codon 816-containing region of the *KIT* gene was amplified using the primers: 5′-TGT GAA CAT CAT TCA AGG CGT AC-3′ (forward) and 5′-ACT CAG CCT GTT TCT GGG AAA CTC-3′ (reverse). PCR conditions were each cycle of 30 s at 93°C, 1 min at 50°C, and 5 min at 72°C for a total of 40 cycles. The resulting 322-bp product was purified from a 2.5% agarose gel using a gel extraction kit (Qiagen) and directly sequenced. On case 3, fluorescence in situ hybridization (FISH) analysis for t(8;21)(q22;q22) on morphologically identified bone marrow mast cells (target FISH) was performed. Briefly, Wright-Giemsa stained bone marrow aspirate smears were scanned with a Bioview Duet Image Analyzer (Bioview, Rehovot, Israel) to identify mast cells for FISH. Following destaining with Carnoy's fixative and digestion with pepsin, slides were co-denatured with t(8;21) probe (Vysis, Downer's Grove, IL, USA). Slides were counterstained with DAPI and analyzed on a BioView Duet Image analyzer. Details of the target FISH technique were described previously [21].

Results

The clinical and pathologic features of the patients are summarized in Table 1. Of the ten patients who are included in this report, cases 1 through 6 were treated at our institutions and four additional cases (cases 7–10) were identified from the literature [17–20]. Cases 1, 2, and 3 of this series were included in previous reports [9, 21].

The patients ranged in age from 26 to 67 years and included three males and seven females. None of the patients had urticaria pigmentosa or other evidence of extramedullary mast cell involvement except for one published case that showed hepatic infiltration with mast cells after AML induction therapy [17]. Symptoms related to mast cell mediator release were not reported in any of the patients. All cases had morphologic and immunophenotypic features of AML with maturation (FAB-M2). Leucocytosis was present at diagnosis in six of seven patients in whom initial blood counts were available. Patient 4 had metastatic breast cancer and had undergone anthracycline-containing combination chemotherapy. She developed SM with t(8;21)(q22;q22) AML 1 year after initiation of chemotherapy. In nine of the ten cases, increased bone marrow mast cells were noted at the time of AML diagnosis In case 4, SM was diagnosed following three cycles of consolidation chemotherapy for AML. In that case, the bone marrow biopsies at diagnosis were reevaluated, but failed to demonstrate coexisting SM. An activating exon 17 *KIT* mutation was detected in seven of nine cases in whom this data is available. Three patients had D816V, two had D816Y, and one carried the D816H mutation. In one case (case 6) the exact mutation was not analyzed while another (case 4) carried an A814S mutation in addition to D816V. It is noteworthy that four of the ten cases had chromosome 9q deletion as an additional cytogenetic abnormality. Of the eight cases where immunophenotype data on the myeloblasts was available by flow cytometry, four of eight cases reported dim expression of CD19 and five of eight cases showed

Table 1 Clinical and pathological features of SM with t(8;21) AML

No.	Ref	Age/sex	Clinical presentation	Bone marrow morphology	Immunophenotype		Cytogenetics	*KIT* Exon 17	Initial treatment	Clinical course
					Blasts	Mast cells				
1	Case 1 [9]	26/M	AML with multilineage dysplasia, WBC—35,400/μL 44% blasts	Hypercellular with Multilineage Dysplasia, 43% myeloblasts Increased mast cells distributed randomly and perivascularly, indented nuclei, normal granularity	CD13, CD33, CD11b, CD34, HLA-DR, CD56 CD7dim CD19 negative	Tryptase	46XY t(8;21) (q22;q22)	D816H	Idarubicin + cytarabine followed by mitoxantrone + etoposide	Induction failure, died of progressive leukemia
2	Case 2 [9]	43/F	AML with multilineage dysplasia	Hypercellularity with multilineage dysplasia, 31% myeloblasts Increased mast cells scattered and perivascular, normal morphology. Mast cell infiltrate prominent after treatment	CD13, CD33, CD34, CD117	Tryptase	46XX t(8;21) (q22;q22)	ND	Daunorubicin + cytarabine followed by HiDAC for 3 cycles	Remission achieved after induction. Relapsed with myeloid sarcoma 1 year after diagnosis. Underwent HSCT but died of relapsed disease 3 years later
3	Case 3 [21]	51/F	FAB-M2 AML	40% myeloblasts, increased mast cells (30% of cellularity) Prominent infiltrate of clustered, spindle-shaped mast cells (80–90% of cellularity) after leukemia remission	CD13, CD33CD, CD38, CD117, HLA-DR, MPO	Trytase, CD2, CD25	46X t(8;21)(q22; q22) del(9) (q12;q22) Monosomy X	D816V	Daunorubicin + cytarabine followed by 2 cycles of HiDAC	AML in complete remission after induction chemotherapy. Persistence of mast cells Allogeneic HSCT from matched sibling after conditioning with TBI and etoposide. AML in remission 4 years after SCT. Persistence but gradual decline of recipient mast cells [carrying t (8;21)] 1 year after HSCT
4	Case 4	54/F	1 year history of metastatic breast cancer treated with anthracycline-based chemotherapy. Therapy-related AML. WBC 58,200/μL, 96% blasts	Complete replacement of diagnosis bone marrow by myeloblasts. No increase in mast cells 70% cellular post-consolidation marrow with 27% blasts and numerous mast cells with indented twisted nuclei and normal granularity	CD34, CD33dim, CD117dim, HLA-DR, CD56, CD19 (dim)	CD25, CD117	46XX t(8;21) (q22;q22)	D816V A814S	Daunorubicin + cytarabine consolidation with HiDAC 3 cycles	Morphologic remission after induction. Bone marrow after consolidation showed relapse. Died of relapsed AML 8 months after diagnosis
5	Case 5	29/F	FAB-M2 AML. WBC —45,400/μL	Hypercellular, 76% myeloblasts with increased mast cells, occasional spindled mast cells present	CD13, CD33 (dim), CD56 (bright), CD34, CD117, CD19 (dim)	CD2, CD25, Tryptase	45XY t(8;21) (q22;q22), del9 (q22) [20]	D816Y	Idarubicin + cytarabine	Induction failure. Died of progressive leukemia 1 year after diagnosis

Table 1 (continued)

No.	Ref	Age/ sex	Clinical presentation	Bone marrow morphology	Immunophenotype		Cytogenetics	*KIT* Exon 17	Initial treatment	Clinical course
					Blasts	Mast cells				
6	Case 6	46/M	FAB-M2 AML WBC 92,600/μL 82% blasts	95% cellularity, 60% myeloblasts, increased mast cells in perivascular and paratrabecular aggregates comprising about 20% of marrow cellularity. Pronounced mast cell infiltrate after treatment	CD13, CD56 CD15[a], CD34, CD38 CD19[a] CD117, HLA-DR	CD117	46XX t(8;21) (q22;q22) del (9)(q22q34)	D816[b]	Idarubicin + cytarabine + Imatinib	Induction failure. Awaiting stem cell transplant
7	Wong et al. [17]	51/F	FAB-M2 AML WBC —2,800/μL 12% blasts	60% myeloblasts and increased mast cells positive for chloro-acetate esterase	MPO Chloroacetate esterase	Chloroacetate esterase	t(8;21)(q22;q22) Monosomy 21	NA	Danorubicin, thioguanine, cytarabine followed by cytarabine and mitoxantrone	Morphologic remission of leukemia after chemotherapy. Persistence of bone marrow mastocytosis and development of hepatosplenomegaly from mast cell infiltration. Died of disease 6 months after diagnosis
8	Escribano et al. [18]	67/F	FAB-M2 AML WBC-25,000/μL 71% blasts	Aspirate revealed 59% myeloblasts, no dysplasia. Increased atypical mast cells, oval nuclei, hypogranular cytoplasm and abnormal granularity	CD13, 33, 117 CD7[a], CD19[a]	Tryptase CD2, 25, 117	Normal conventional cytogenetics (46XX), FISH: t(8;21)(q22; q22)	D816V not detected [c]	Idarubicin + cytarabine 2 cycles	Morphologic remission of AML after 2 cycles of induction. Persistent bone marrow mastocytosis. Relapsed 1 year after diagnosis and died of disease in second relapse 2 years after diagnosis
9	Bernd et al. [19]	48/M	FAB-M2 AML	Hypercellularity, sheets of myeloblasts Loosely scattered mast cells at diagnosis. Mastocytosis prominent after leukemic remission	Myeloperoxidae and chloroacetate esterase	CD25, CD117, tryptase	46XY t(8;21;12) (q22;q22;q24)	D816V	Idarubicin + cytarabine for 3 cycles, HiDAC one cycle	Morphologic remission of AML after one cycle of chemotherapy. AML remained in remission 20 months after diagnosis. Bone marrow mastocytosis persisted for 18 months
10	Nagai et al. [20]	31/F	WBC—18,600/μL 69% blasts	Hypercellularity, 54% myeloblasts, multifocal dense infiltrates of mast cells at diagnosis. Mastocytosis pronounced after induction chemotherapy	Positive: CD13, CD34, CD56, CD117, HLA-DR	CD25, CD117	46XX, t(8;21) (q22;q22) del9 (q22;q34)	D816Y	Idarubicin + cytarabine followed by mitoxantrone + cytarabine	Induction failure after 2 cycles of chemotherapy Allogeneic HSCT from matched sibling after conditioning with TBI and cyclophosphamide Persistent bone marrow mastocytosis but remission of leukemia over 1 year after HSCT

ND not detected, *FAB* French American British, *WBC* white blood cell, *HiDAC* high dose cytarabine, *HSCT* hematopoietic stem cell transplantation, *TBI* total body irradiation, *NA* data not available

[a] Denotes expression on subset of blasts

[b] Exact mutation not analyzed

[c] Not known if other KIT mutations were examined

CD56 expression (Table 1). Bone marrow pathology of a representative case is shown in Fig. 1.

All patients were initially treated with AML induction chemotherapy that contained an anthracycline and cytarabine. Four of the ten patients failed to achieve a morphologic remission after induction chemotherapy. Six of the ten patients have died of progressive or relapsed leukemia and one patient remains with active disease awaiting allogeneic HSCT. The two long-term survivors (cases 3 and 10) in this report had both undergone allogeneic HSCT from matched siblings after radiation-based high-dose conditioning. In these two patients, recipient-derived bone marrow mast cells were detected up to a year after HSCT, but the leukemia remained in durable remission.

Discussion

In this report, we have summarized our experience and reviewed the published literature on SM that coexists with t(8;21)(q22;q22) AML. *KIT* mutations are the most common additional genetic abnormality in t(8;21) AML and range in their incidence from 26% to 47% in various reports [22–24]. However, among the t(8;21) AML with *KIT* mutations, the number of cases that have concurrent SM appears to be extremely rare. Hence, it appears that specific genetic events in addition to activating *KIT* mutations and t(8;21) are required for development of mastocytosis. Although it can be postulated that these additional genetic events may promote mast cell differentiation from leukemic progenitors, the nature of these additional genetic aberrations remains unknown.

Studies examining the relationship between mast cells and leukemic blasts have shown that the neoplastic mast cells of SM associated with t(8;21) carry the *RUNX1-RUNX1T1* translocation, thereby proving their derivation from the leukemic clone. This was demonstrated in case 3 of this series by target FISH, the details of which have been published elsewhere [21]. Similar findings were noted in another published case that is included in the current series (case 10, Nagai et al.) where *KIT* mutation as well as *RUNX1-RUNX1T1* translocation was detected in recipient-derived clonal mast cells that persisted after allogeneic HSCT [20]. In both these cases, the recipient-derived mast cells gradually declined and the AML remained in remission. It is unclear if this phenomenon represents gradual apoptosis of these mast cells or progressive elimination of leukemic progenitors due to graft-versus-leukemia effect.

We sought to examine if there were other distinct cytogenetic or pathologic features that were associated with SM and t(8;21) AML. Deletion of chromosome 9q was an additional cytogenetic finding in four of the ten cases. Del (9q) has been previously reported as part of a complex phenotype in another case of t(8;21) positive myelomastocytic leukemia (AML with increased bone marrow mast cells not meeting criteria for SM) [26]. In addition, del (9q) is the most common additional cytogenetic abnormality in

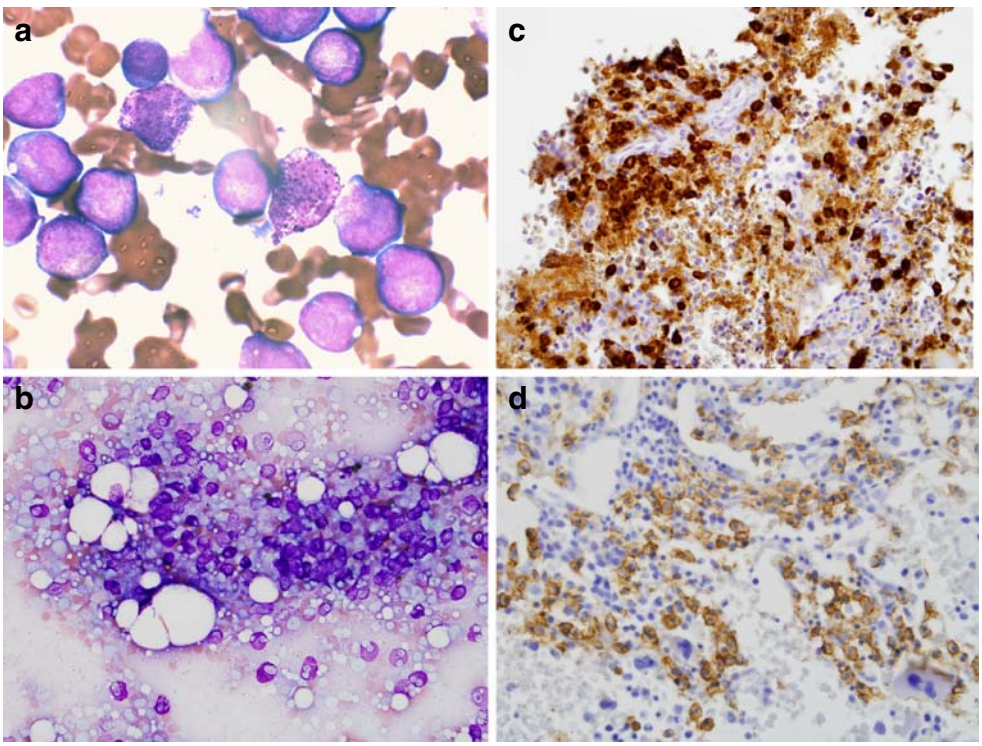

Fig. 1 **a** Pretreatment bone marrow aspirate (case 3) showing predominantly myeloblasts admixed with rare mast cells. Note the hypergranular cytoplasm within the mast cells (Wright-Giemsa, ×500). **b** Day 14 post-treatment bone marrow aspirate (case 3) with prominent mast cell infiltrate (Wright-Giemsa, ×200). **c** Immunohistochemistry for tryptase (case 3) highlights the mast cell infiltrate (×200). **d** Mast cells show expression of CD25 (case 3), a characteristic feature of neoplastic mast cells (×200)

t(8;21) AML and has been reported in 7–14% of pediatric cases and 9.7% of adult cases [27]. In comparison, del (9q) appears to be more frequent in t(8;21) with associated SM, suggesting that this deletion may play a role in the pathogenesis of SM. Recently, *TLE1* and *TLE4* have been identified as critical genes in the commonly deleted 9q region in t(8;21) AML [28]. In vitro experiments using Kasumi-1 cell line showed that these genes behave as tumor suppressors and knockdown of *TLE1* or *TLE4* increased the rate of cell division of the *AML1-ETO* expressing Kasumi-1 cell line while forced expression of either caused apoptosis and cell death [28].

The precise incidence of SM coexisting with t(8;21) AML is unknown. In previous reports, authors have cautioned that in some cases of AML with coexisting SM, the diagnosis of SM maybe missed on the initial bone marrow evaluation due to the excess numbers of blasts which mask the underlying mast cells and the tendency of mast cells to localize within stroma of bone marrow particles in aspirate smears [9]. The bone marrow mast cell infiltrate appears to become more evident when the leukemic blasts decrease after therapy as was seen in this report (Fig. 1b). This prominence of the mast cell infiltrate after chemotherapy may also be due to the poor sensitivity of the mast cells to leukemia chemotherapy as evidenced by their persistence even after high-dose chemotherapy conditioning for allogeneic HSCT [20]. Infiltration of extramedullary tissues with mast cells, as well as symptoms due to mast cell mediator release, appear to be distinctly uncommon in cases of SM associated with t(8;21) AML. This may be due to the lack of functionality of these neoplastic MC as a result of the leukemic aberrations they carry.

AML with t(8;21)(q22;q22) as the sole cytogenetic abnormality in general have a favorable outcome when treated with consolidation regimens containing high-dose cytarabine [29, 30]; however, studies have shown that only 50% of t(8;21) AML patients are alive at 5 years [27]. D816 *KIT* mutations were detected in 10.5% of patients with t(8;21) AML in one study [17]. The presence of *KIT* mutations (D816 and others) may explain the poor prognosis of a subset of t(8;21) patients as activating exon 17 *KIT* mutations have now been shown to be a major adverse prognostic factor for event-free and overall survival in t(8;21) AML [14–17] and a predictor of higher relapse risk [15]. The number of patients with mutant *KIT* who had SM in addition has not been reported in any of these studies, which may be an indicator of its extreme rarity. Interestingly, in previous studies it has been reported that 91–100% of t(8;21) AML patients with *KIT* mutations achieved complete remission after chemotherapy [15, 25]. However, in our current series induction failure occurred in four of ten patients. This observation again re-emphasizes the fact that SM associated with AML has a grave prognosis.

It is worth noting that of the ten patients (Table 1) only two patients achieved a durable remission of AML. Both of these patients had undergone allogeneic HSCT. One of our patients (case 3) is in continuous remission 4 years after allogeneic HSCT. Sperr et al. have reported a patient with myelomastocytic leukemia and t(8;21) AML who relapsed after a reduced intensity HSCT, but achieved a lasting remission following high-dose conditioning and a second HSCT from the same donor, thereby suggesting that conditioning intensity may be important [26]. Although data are very limited, the dismal results with conventional chemotherapy suggests that allogeneic HSCT should be an early consideration in SM associated with t(8;21) AML in patients who are suitable candidates. The D816V *KIT* mutation is resistant to the tyrosine kinase inhibitor imatinib [31]. Dasatinib, to which *KIT* D816V is sensitive, may have a role in the therapy of these cases as evidenced by in vitro data as well as its in vivo activity of this drug in recent reports of SM, including a patient with SM-AML [32–34]. Other tyrosine kinase inhibitors like midostaurin (PKC 412) and nilotinib (AMN 107)) that are capable of inhibiting activating *KIT* D816V may also have potential in the treatment of t(8;21) AML that carry this mutation [35, 36].

In conclusion, SM associated with t(8;21) AML is extremely rare and carries a dismal prognosis. During evaluation of t(8;21)(q22;q22) AML, care should be taken to look for coexisting SM in the initial and subsequent bone marrow specimens since the mast cell infiltrate may be subtle and easily overlooked. This will help identify a subset of t(8;21) AML patients with a particularly poor prognosis.

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References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW eds (2008) WHO classification of tumors of haematopoietic and lymphoid tissues. IARC, Lyon
2. Asou N (2003) The role of a Runt domain transcription factor AML1/RUNX1 in leukemogenesis and its clinical implications. Crit Rev Oncol Hematol 45:129–150
3. Tenen DG (2003) Disruption of differentiation in human cancer. AML shows the way. Nat Rev Cancer 3:89–101
4. Yuan Y, Zhou L, Miyamoto T et al (2001) AML-ETO expression is directly involved in the development of acute myeloid leukemia in the presence of additional mutations. Proc Natl Acad Sci USA 98:10398–10403
5. Wang YY, Zhou GB, Yin T et al (2005) AML1-ETO and C-KIT mutation/overexpression in t(8;21) leukemia: implication in

stepwise leukemogenesis and response to Gleevec. Proc Natl Acad Sci USA 102:1104–1109
6. Kuchenbauer F, Feuring-Buske M, Buske C (2005) AML1-ETO needs a partner. Cell Cycle 4:1716–1718
7. Grisolano JL, O'Neal J, Cain J, Tomasson MH (2001) An activated receptor tyrosine kinase, TEL/PDGF cooperates with AML1/ETO to induce acute myeloid leukemia in mice. Proc Natl Acad Sci USA 100:9506–9511
8. Rhoades KL, Hetherington CJ, Harakawa N et al (2000) Analysis of the role of AML-ETO in leukemogenesis using an inducible transgeneic mouse model. Blood 96:2108–2115
9. Pullarkat VA, Bueso-Ramos C, Lai R et al (2003) Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease: analysis of clinicopathologic features and activating c-kit mutations. Am J Hematol 73:12–17
10. Sperr WR, Horny H-P, Valent P (2002) Spectrum of associated clonal hematologic non-mast cell lineage disorders occurring in patients with systemic mastocytosis. Int Arch Allergy Immunol 127:140–142
11. Sperr WR, Horny HP, Lechner K, Valent P (2000) Clinical and biologic diversity of leukemias occurring in patients with mastocytosis. Leuk Lymphoma 37:473–486
12. Travis WD, Li CY, Yam LT, Bergstralh EJ, Swee RG (1988) Significance of systemic mast cell disease with associated hematologic disorders. Cancer 62:965–972
13. Horny HP, Parwaresch MR, Lennert K (1985) Bone marrow findings in systemic mastocytosis. Human Pathol 16:808–814
14. Cairoli R, Beghini A, Grillo G et al (2006) Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. Blood 107:3463–3468
15. Paschka P, Marcucci G, Ruppert AS et al (2006) Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv (16) and t(8;21): a Cancer and Leukemia Group B Study. J Clin Oncol 24:3904–3911
16. Schnittger S, Kohl TM, haferlach T, Kern W, Hiddemann W, Spiekermann K, Schoch C (2006) KIT-D816 mutation in AML1-ETO positive AML are associated with impaired event-free and overall survival. Blood 107:1791–1799
17. Wong KF, Chan JKC, Chan JCW, Kwong YL, Ma SK, Chow TC (1991) Concurrent acute myeloid leukemia and systemic mastocytosis. Am J Hematol 28:243–244
18. Escribano L, Garcia-Montero A, Nunez-Lopez R et al (2004) Systemic mastocytosis associated with acute myeloid leukemia: case report and implications for disease pathogenesis. J Allergy Clin Immunol 114:28–33
19. Bernd HW, Sotlar K, Lorenzen J et al (2004) Acute myeloid leuke mia with t(8;21) associated with "occult" mastocytosis. Report of an unusual case and review of the literature. J Clin Pathol 57:324–328
20. Nagai S, Ichikawa M, Takahashi T, Sato H, Yokota H, Oshima K, Izutsu K et al (2007) The origin of neoplastic mast cells in systemic mastocytosis with AML1/ETO positive acute myeloid leukemia. Exp Hematol 35:1747–1752
21. Pullarkat V, Bedell V, Kim Y et al (2007) Neoplastic mast cells in systemic mastocytosis associated with t(8;21) acute myeloid leukemia are derived from the leukemic clone. Leuk Res 31:261–265
22. De J, Zanjani R, Hibbard M et al (2007) Immunophenotype profile predictive of KIT activating mutations in AML-ETO leukemia. Am J Clin Path 128:550–557
23. Beghini A, Cairoli R, Morra E, Larriza L (1998) In vivo differentiation of mast cells from acute myeloid leukemia blasts carrying novel activating ligand-independent c-kit mutation. Blood Cells Mol Dis 24:262–270
24. Beghini A, Peterlongo P, Ripamonti CB et al (2000) C-Kit mutations in core binding factor leukemias [letter]. Blood 95:726–727
25. Nanri T, Matsuno N, Kawakita T, Suzushima H, Kawano F, Mitsuya H, Asou N (2005) Mutations in the receptor tyrosine kinase pathway are associated with clinical outcome in patients with acute myeloblastic leukemia harboring t(8;21) (q22;q22). Leukemia 19:1361–1366
26. Sperr WR, Drach J, Hauswirth AW et al (2005) Myelomastocytic Leukemia: evidence for the origin of mast cells from the leukemia clone and eradication by allogeneic stem cell transplantation. Clin Cancer Res 11:6787–6792
27. Marcucci G, Mrozek K, Ruppert AS et al (2003) Prognostic factors and outcome of core binding factor acute myeloid leukemia patients with t(8;21) differ from those of patients with inv(16): a Cancer and Leukemia Group B study. J Clin Oncol 23:5705–5717
28. Dayyani F, Wang J, Yeh J-R J (2008) Loss of TLE1 and TLE4 from the del(9q) commonly deleted region in AML cooperate with AML1-ETO to affect myeloid cell proliferation and survival. Blood 111(8):4338–4347
29. Bloomfield CD, Lawrence D, Byrd JC et al (1998) Frequency of prolonged remission duration after high dose cytorabine intensification in acute myeloid leukemia varies by cytogenetic subtype. Cancer Res 58:4173–4179
30. Byrd JC, Dodge RK, Carroll A et al (1999) Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure free and overall survival when repetitive cycles of high-dose cytarabine are administered. J Clin Oncol 17:3767–3775
31. Frost MJ, Ferrao PT, Hughes TP, Ashman LK (2002) Juxtamembrane mutant V560GKit is more sensitive to Imatinib (STI 571) compared with wild-type c-KIT whereas the kinase domain mutant D816VKit is resistant. Mol Cancer Ther 1:1115–1124
32. Shah NP, Lee FY, Luo R et al (2006) Dasatinib (BMS-354825) inhibits KITD816V, an imatinib-resistant activating mutation that triggers neoplastic growth in most patients with systemic mastocytosis. Blood 108:286–291
33. Purtill D, Cooney J, Sinnah R et al (2008) Dasatinib therapy for systemic mastocytosis: four cases. Eur J Haematol 80:456–458
34. Ustun C, Corless CL, Savage N et al (2008) Chemotherapy and dasatinib induce long-term hematologic and molecular remission in systemic mastocytosis with acute myeloid leukemia with KIT ^{D816V}. Leuk Res (Epub ahead of print)
35. Gotlib J, Berube C, Growney JD et al (2005) Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V *KIT* mutation. Blood 106:2865–2870
36. Von Bubnoff N, Gorantla SHP, Kancha RK et al (2005) The systemic mastocytosis-specific activating cKit mutation D816V can be inhibited by the tyrosine kinase inhibitor AMN107. Leukemia 19:1670–1671