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ORIGINAL ARTICLE

Acute myeloid leukemia with t(8;16)(p11.2;p13.3) /*KAT6A-CREBBP* in adults

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Abstract

t(8;16)(p11.2;p13.3)/*KAT6A-CREBBP* is a rare recurrent cytogenetic abnormality associated with acute myeloid leukemia (AML). We report 15 cases with t(8;16)(p11.2;p13.3). All patients were adult and had AML: 13 women and 2 men, with a median age of 50 years. Ten patients had a history of malignancy and received cytotoxic therapies before therapy-related AML (t-AML), and five patients had de novo AML. All cases of AML showed monoblastic ($n = 12$) or myelomonocytic ($n = 3$) differentiation. Hemophagocytosis was observed in seven patients. All patients had t(8;16) in the stemline: seven had t(8;16) as the sole abnormality, two had one additional abnormality, and six had a complex karyotype. *KAT6A/CREBBP* rearrangement was confirmed by fluorescence in situ hybridization in 13 patients who had material available for analysis. All patients received induction chemotherapy, and 11 achieved complete remission after first induction. At the time of last follow-up, nine patients (eight t-AML and one de novo AML) died and six were alive, with a median overall survival of 18.2 months. The patients with de novo AML and/or patients with non-complex karyotype showed an "undefined" overall survival. We conclude that t(8;16)(p11.2;p13.3) commonly exhibits monoblastic or myelomonocytic differentiation and commonly arises in patients with a history of cancer treated with cytotoxic therapies. Patients with de novo AML with t(8;16) or t-AML with t(8;16) without adverse prognostic factors (e.g., complex karyotype) have a good outcome.

Keywords Acute myeloid leukemia · t(8;16)(p11.2;p13.3) · *KAT6A* · *CREBBP* · Therapy-related

Introduction

Acute myeloid leukemia (AML) with t(8;16)(p11.2;p13.3)/*KAT6A-CREBBP* is an uncommon entity, accounting for 0.2 to 0.4% of all cases of AML [1–3]. Approximately 100 AML cases with t(8;16)(p11.2;p13.3) have been reported, mainly in single case reports and a few case series from multiple centers and including adult and pediatric patients [1, 3–9]. AML with t(8;16)/*KAT6A-CREBBP* is often associated with monocytic or myelomonocytic differentiation, leukemia cutis, hemophagocytosis, and disseminated intravascular coagulation (DIC) [1, 3, 4, 9]. t(8;16)/*KAT6A-CREBBP* is more frequently associated with therapy-related AML (t-AML, 1.6%) [1] and neonatal AML [9]. AML with t(8;16) has been reported to be associated with a poor outcome [1, 3, 4]; however, spontaneous remission has been observed in neonates [9–12].

KAT6A (also known as *MOZ* or *MYST3*) is located on chromosome 8p11.2 and is composed of 17 exons. *KAT6A* encodes the monocytic leukemia zinc finger protein, a histone acetyltransferase of the *MYST* family that modulates gene transcription through activation of the *RUNX1* (*AML1*) transcription factor complex [13]. *CREBBP* is located on chromosome 16p13.3 and is composed of 31 exons. *CREBBP* encodes a protein that is widely expressed and plays a transcription regulatory role by interaction with several proteins with central cell cycle functions [14]. Like KAT6A, CREBBP has an intrinsic histone acetyltransferase activity and aberrant chromatin acetylation may lead to leukemogenesis [15]. *KAT6A* and *CREBBP* are common gene partners, but both genes are also involved in other translocations with different partners in AML, e.g., *KAT6A* in inv(8)(p11q13)/*KAT6A-NCOA2*, t(8;19)(p11;q13)/*KAT6A-?*, t(8;20)(p11;q13)/*KAT6A-*

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NCOA3; and t(8;22)(p11;q13)/*KAT6A-EP300*; and *CREBBP* in t(10;16)(q22;p13)/*KAT6B-CREBBP* and t(11;16)(q23;p13)/*KMT2A-CREBBP*, respectively.

Therapy-related myeloid neoplasms (t-MNs) occur as a late complication of exposure to cytotoxic therapy, including chemotherapy and/or radiation therapy used in treating malignant or non-malignant diseases [16, 17]. Patients with t-MNs usually have a very poor outcome, with a median overall survival (OS) of 8 to 14 months [16, 17]. The primary malignancies often associated with t-MNs include breast cancer and hematolymphoid malignancies [17]. Topoisomerase II inhibitors, which have been widely used in the treatment of breast cancer [18], are known to be associated with balanced translocations in t-AML [16, 17]. Among the balanced translocations, those involving 11q23/*KMT2A* are the most common [16, 17], whereas t(8;16)(p11.2;p13.3) is less frequently detected in t-MNs.

Due to the rarity of AML associated with t(8;16)(p11.2;p13.3), most cases have been reported as signal cases or case series from multiple centers. The outcomes of this neoplasm have varied greatly in different reports and in different age groups. In this study, we describe detailed clinicopathologic, molecular, cytogenetic, and outcome data of 15 adult patients from a single institution with AML t(8;16)/*KAT6A-CREBBP*.

Materials and methods

Case selection

We searched the cytogenetic archives of our institution during January 1, 1998, through December 31, 2018, for cases with t(8;16)(p11.2;p13.3). Clinical, morphologic, immunophenotypic, molecular, and cytogenetic data were reviewed and analyzed. This retrospective study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center and was conducted in accordance with the Declaration of Helsinki.

Morphologic examination

Bone marrow specimens collected at the time of t(8;16)(p11.2;p13.3) detection were obtained for all patients. Wright–Giemsa-stained peripheral blood and bone marrow aspirate smears, and hematoxylin and eosin–stained sections of bone marrow core biopsy specimens were reviewed in all cases.

Immunophenotypic analysis

Bone marrow aspirate specimens were subjected to standard eight-color flow cytometry immunophenotype analysis as described previously [19], and antibodies against the following antigens were used: CD2, CD3, CD4, CD5, CD7, CD9, CD10, CD11b, CD13, CD14, CD19, CD20, CD22, CD25, CD34, CD38, CD41, CD56, CD64, CD79b, CD117, CD123, HLA-DR, myeloperoxidase (MPO), and terminal deoxynucleotide transferase (TDT) (BD Biosciences, San Jose, CA). Cytochemical stains for myeloperoxidase and non-specific esterase were performed on all diagnostic bone marrow aspirate smears.

Conventional cytogenetics and FISH analyses

Conventional G-banded chromosomal analysis was performed on unstimulated 24-h and 48-h bone marrow aspirate cultures using standard techniques. Twenty metaphases were analyzed, and the results were reported using the 2016 International System for Human Cytogenetics Nomenclature (ISCN 2016). A complex karyotype was defined as ≥ 3 chromosomal abnormalities.

Fluorescence in situ hybridization (FISH) analysis was performed with Wright–Giemsa-stained bone marrow smears using dual-color dual fusion FISH probes for *KAT6A* (labeled with green) and *CREBBP* (labeled with orange) (CytoTest, Rockville, MD) according to the manufacturer's instructions.

Molecular mutation studies

Molecular analysis was performed on a subset of patients as a part of the routine clinical workup. Targeted next-generation sequencing (NGS) studies using panels of genes commonly altered in hematopoietic neoplasms were performed in four patients, using a 28-gene or 81-gene panel (Supplemental material 1) as described previously [20].

Statistical analysis

Kaplan–Meier method was used to estimate OS from the date of t(8;16)(p11.2;p13.3) detection to the date of death from any cause, or censored at last follow-up date for alive patients. $p < 0.05$ was considered to be statistically significant.

Results

Clinical features

The clinical features are summarized in Table 1. A total of 15 cases with t(8;16)(p11.2;p13.3) were identified. All patients were adult and had AML: 13 women and 2 men, with a median age of 50 years (range, 19–62 years). All patients had t(8;16)(p11.2;p13.3) detected at the initial diagnosis of AML. Three patients also showed extramedullary disease (leukemia cutis), and three patients had DIC.

Table 1 Clinical features of patients with AML with t(8;16)(p11.2;p13.3)

Case	Age/sex	Prior malignancy and treatments		Int	At t(8;16) detection			Treatment of AML	Outcomes		
		Diagnosis	Therapies		WHO	FAB	Blast %		CR	Status	OS
1	62/F	Breast cancer	Radiation, Chemo	19	t-AML	M5a	84	Idarubicin, cytarabine, zofran methylprednisolone	Yes	Alive	133
2	53/F	Breast cancer	Tamoxifen herceptin, radiation	26	t-AML	M5a	80	Clofarabine, idarubicin, cytarabine, SCT	Yes	Dead	23
3	49/F	Breast cancer	Radiation, Chemo	4	t-AML	M5a	81	Clofarabine, idarubicin, cytarabine	No	Dead	18
4	43/F	Breast cancer	Chemo	16	t-AML	M5a	88	7 + 3 induction, crenolanib	No	Dead	9
5	59/F	Breast cancer	Chemo	17	t-AML	M5a	70	Idarubicin, cytarabine, SCT	Yes	Dead	9
6	47/F	DLBCL, AIDS	Chemo	153	t-AML	M5a	74	Cladribine, idarubicin, cytarabine	Yes	Dead	14
7	57/F	DLBCL, Crohn's disease	Chemo	41	t-AML	M5a	98	Clofarabine, idarubicin cytarabine	Partial	Dead	1
8	49/F	DLBCL, autoimmune hepatitis	Chemo radiation	9	t-AML	M4	35	Cytarabine	Yes	Alive	97
9	45/F	Extranodal MZL	Chemo	13	t-AML	M5a	64	Idarubicin, cytarabine, Zarnestra	Yes	Dead	9
10	50/F	Liposarcoma	Chemo	47	t-AML	M5a	74	Clofarabine, idarubicin, cytarabine, SCT	Yes	Dead	6
11	55/F	No	No	NA	AML	M5a	83	Idarubicin, cytarabine, sorafenib, SCT	Yes	Alive	117
12	19/F	No	No	NA	AML	M5a	84	Fludarabine, idarubicin, cytarabine, SCT	Yes	Alive	43
13	56/F	No	No	NA	AML	M5a	59	Fludarabine, idarubicin, cytarabine, decitabine	Yes	Alive	113
14	51/M	No	No	NA	AML	M4	54	Daunorubicin,cytarabine	Yes	Alive	224
15	28/M	No	No	NA	AML	M4	63	7 + 3 induction	No	Dead	7

AIDS acquired immune deficiency syndrome, *AML* acute myeloid leukemia, *Chemo* chemotherapy, *CR* complete remission, *DLBCL* diffuse large B cell lymphoma, *F* female, *Int* interval (month) from the initiation of cytotoxic therapy to t(8;16)(p11.2;p13.3) detection, *M* male, *M4* acute myelomonocytic leukemia, *M5a* acute monoblastic leukemia, *MZL* marginal zone lymphoma, *NA* not available, *OS* overall survival (months), *SCT* stem cell transplant, *t* therapy-related

Ten patients had a history of various malignancies, including breast carcinoma ($n = 5$), diffuse large B cell lymphoma ($n = 3$), marginal zone lymphoma ($n = 1$), and liposarcoma ($n = 1$). The median interval from the initiation of cytotoxic therapy to diagnosis of AML was 18 months (range, 4–153 months). All ten patients received chemotherapy, including eight with topoisomerase II inhibitors. Three patients (case nos. 6–8) had autoimmune diseases or acquired immunodeficiency syndrome (AIDS). Five patients had no significant medical history (Table 1).

Morphologic findings

The median blast count was 74% (range, 35–98%). All patients presented with acute monoblastic leukemia (AML-M5a) ($n = 12$) or acute myelomonocytic leukemia (AML-M4) ($n = 3$) (Fig. 1a, b). Mild dysplasia was observed in three patients. Erythrophagocytosis or hemophagocytosis was seen in seven patients (Fig. 1c, d). Cytochemical staining of bone marrow aspirate smears showed that the blasts were positive for myeloperoxidase ($n = 10$) and nonspecific esterase ($n = 14$) (Fig. 1e, f).

Immunophenotypic findings

The blasts were assessed in all cases and were positive for the following myeloid and/or monocytic markers: CD4 (7/7), CD33 (15/15), HLA-DR (14/15), CD13 and CD64 (13/15), CD15 (10/15), MPO (9/15), CD14 (7/15), CD56 (6/11), CD117 (2/15), and CD34 (1/15). All cases were negative for CD7.

Cytogenetic and molecular findings

The conventional cytogenetic features of the cases of AML with t(8;16)(p11.2;p13.3) are summarized in Table 2 (Fig. 2a).

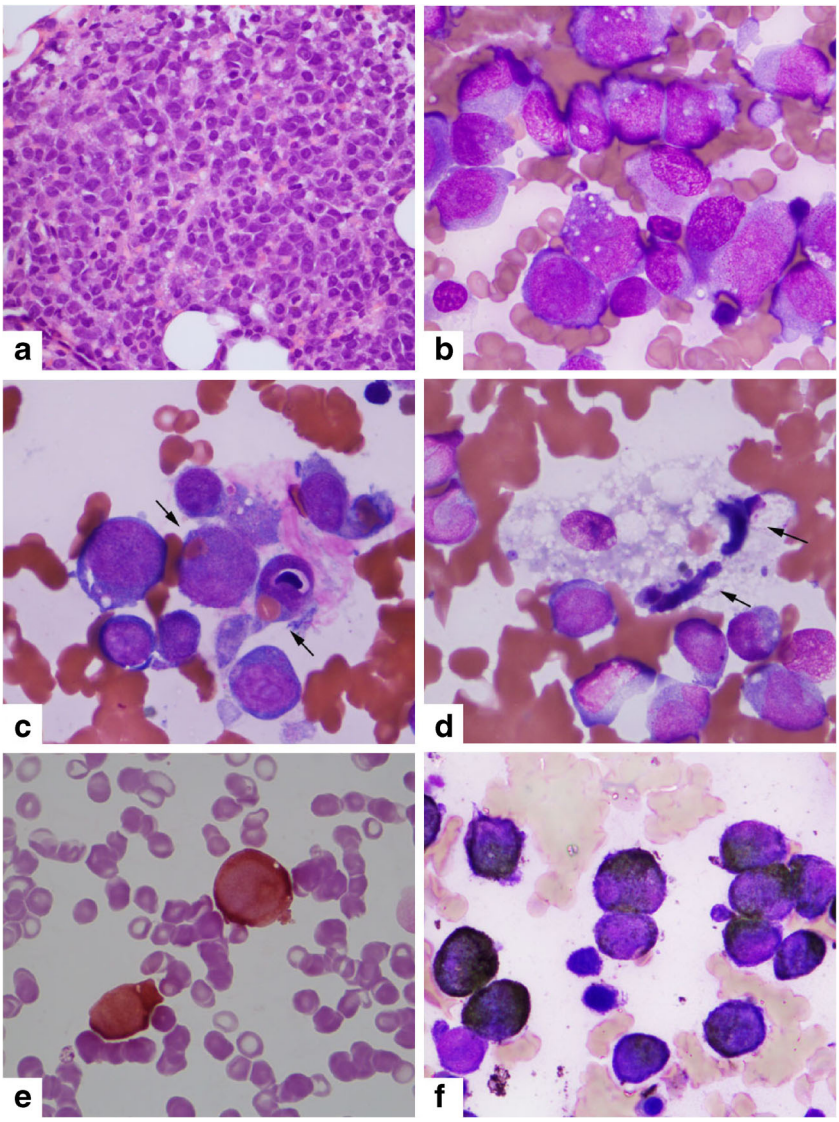

Fig. 1 Morphological findings. **a** Bone marrow clot section showed sheets of immature cells (H&E, × 400). **b** Bone marrow aspirate smear showed many blasts with monocytic differentiation (× 1000). **c** Two cells showed erythrophagocytosis (× 1000). **d** A macrophage showed hemophagocytosis (× 1000). **e** Blasts were positive for non-specific esterase (× 1000). **f** Blasts were positive for myeloperoxidase (× 1000)

Table 2 Cytogenetic and molecular mutation findings

Case	Cytogenetic findings		Molecular mutation	
	Karyotype	FISH for *KAT6A/CREBBP*	Positive	Negative
1	46,XX,t(8;16)(p11.2;p13.3)[11]/46,X,add(X)(q22),t(8;16)(p11.2;p13.3)[6]	Positive	None	*FLT-3*, *KIT*, *RAS*
2	46,XX,t(8;16)(p11.2;p13)[11]/46,idem,t(1;2)(p34;q12),ins(11;17)(q13;q11.2q23)[7]//46,XY[2]	Positive	None	*FLT3*, *NPM1*
3	46,XX,t(8;16)(p11.2;p13.3)[20]	NA	None	*FLT3*, *RAS*
4	47,XX,+8,t(8;16)(p11.2;p13.3)[4]/47,idem,t(2;6)(q33;p12),ins(3:?)(q12:?),del(13)(q12q14)[11]/ 44~47,idem,+mar[cp5]	Positive	*FLT3*	All others (28-gene NGS)
5	46,X,add(X)(p22.1),t(8;16)(p11.2;p13.3)[2]/45–47,idem,del(7)(q32q34),+mar[cp9] 46,XX,add(7)(q32),t(8;16)(p11.2;p13.3),add(9)(p22),add(21)(p11.2)[cp9]	Positive	None	*FLT3*, *RAS*
6	46,XX,add(1)(p36.3),t(8;16)(p11.2;p13.3)[20]	Positive	*DNMT3A, SMC1A, KDM6A*	All others (81-gene NGS)
7	46,XX,t(8;16)(p11.2;p13.3)[20]	Positive	None	*CKIT*, *FLT3*, *RAS*
8	46,XX,t(8;16)(p11.2;p13.3)[6]/46,XX[14]	Positive	None	*FLT3*
9	46,XX,t(8;16)(p12;p13.3)[8]/46,idem,del(7)(q22q32)[4]/46,idem,add(19)(p13)[2]/46,XX[6]	Positive	None	*FLT3*, *RAS*
10	46,XX,i(8)(q10),t(8;16)(p11.2;p13.3),der(17)del(17)(p11.2p13)del(17)(q21q25)[20]	Positive	ND	ND
11	46,XX,t(8;16)(p11.2;p13.3)[20]	Positive	None	*IDH*, *CEBPA*, *CKIT*, *RAS*, *NPM1*, *FLT3*
12	46,XX,t(8;16)(p11.2;p13.3),inv.(9)(p12q13)[20]	NA	*ASXL1*	All others (28-gene NGS)
13	46,XX,t(8;16)(p11.2;p13.3)[4]/46,XX[16]	Positive	None	*CKIT*, *FLT3*, *RAS*
14	46,XY,t(8;16)(p11.2;p13.3)[14]/46,XY[6]	Positive	ND	ND
15	46,XY,der(3)t(3;8)(q27,q13),del(6)(p22),t(8;16)(p11.2;p13.3),del(10)(q21q25),add(13)(p11.2),del(16)(p12),del(20)(p11.2),del(20)(q11.2q13.3) [4]/46,idem,del(1)(p35p36.3),del(15)(q23),add(19)(p13.1)[2]/ 46,XY,t(8;16)(q27;q13),del(12)(q21q24.1),del(13)(q21q31),-16,der(19)t(1;19)(q32;p13.3),+mar[3]/ 46,XY,del(6)(p22),t(8;16)(p11.2;p13.3)[cp2]/46,XY[9]	Positive	*EGFR, PTPN11*	All others (28-gene NGS)

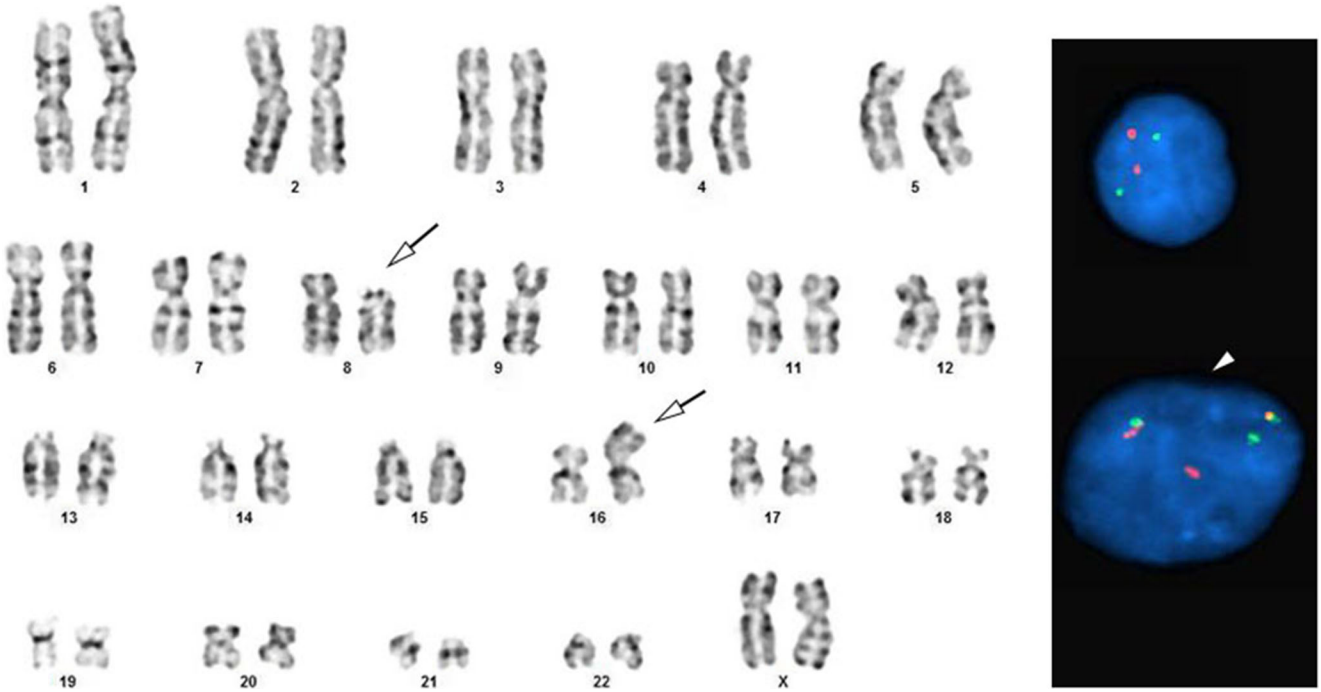

Fig. 2 Cytogenetic findings. **a** Karyotype of 46,XX,t(8;16)(p11.2;p13.3). **b** FISH analysis using dual-color dual fusion *KAT6A* (green)/*CREBBP* (orange) showing 2 fusion (yellow) signals, indicating *KAT6A/CREBBP* rearrangement

All patients had t(8;16) in the stemline; seven had t(8;16) as a sole chromosomal abnormality and eight exhibited additional cytogenetic aberrations: two patients had one and six patients had two or more additional aberrations (complex karyotype).

FISH for *KAT6A/CREBBP* rearrangement was performed in 13 patients who had material available. In all patients, two fusion (yellow) signals, consistent with *KAT6A/CREBBP* rearrangement, were observed (Fig. 2b).

Molecular mutations are summarized in Table 2. Four patients had NGS analysis, and all four showed at least one gene mutation; each gene mutation was detected in only one patient each.

Treatments and outcomes

After diagnosis of AML, all patients received "7 + 3" induction chemotherapy and five also underwent allogeneic stem cell transplant (SCT) (Table 1). Eleven patients achieved complete remission (CR) after the first induction. At the time of last follow-up, nine patients died, including eight t-AML and one de novo AML, with a median survival of 18.2 months (Fig. 3a). Patients with de novo AML had a superior survival compared with patients with t-AML (undefined vs. 11.4 months, $p = 0.0651$) (Fig. 3b). Patients had t(8;16) as the sole abnormality or plus one additional abnormality had a superior survival compared to patients with t(8;16) plus two or more abnormalities (a complex karyotype) (undefined vs. 8.9 months, $p = 0.0048$) (Fig. 3c).

Discussion

Here, we report the largest cohort of cases of adult AML with t(8;16)(p11.2;p13.3)/*KAT6A-CREBBP* from a single institution. In this cohort, all patients had t(8;16)/*KAT6A-CREBBP* in the stemline, including seven patients with t(8;16) as the sole abnormality, supporting a critical role for t(8;16)/*KAT6A-CREBBP* in the pathogenesis of these neoplasms. AML with t(8;16)(p11.2;p13.3)/*KAT6A-CREBBP* shows many clinical and pathological features that overlap with AML with t(11q23;v)/*KMT2A(MLL)* rearrangements. Both forms of AML frequently exhibit extramedullary presentations and monocytic/monoblastic or myelomonocytic differentiation; both are commonly associated with newborn/infant AML or t-AML with topoisomerase-II inhibitor exposure [6, 16]. These similarities may be explained by the important roles the *KAT6A-CREBBP* and *KMT2A* fusion genes play in histone modification. It is tempting to speculate that *KMT2A* and *KAT6A-CREBBP* share similar signaling pathways during AML pathogenesis. Studies have shown that the gene expression profiles of patients with t(8;16)/*KAT6A-CREBBP* clustered close to AML with t(11q23)/*KMT2A* and both share commonly expressed genes [1, 9]. Genes with higher expression in both AML with t(8;16)/*KAT6A-CREBBP* and AML with t(11q23;v)/*KMT2A* include *HOXA3*, *HOXA4*, *HOXA5*, *HOXA6*, *HOXA7*, *HOXA9*, *HOXA10*, *PBX3*, *MEIS1*, and *HNMT* [1]. In addition, an N terminal truncated BRE (brain and reproductive organ-expressed) protein is highly expressed in over 50% of cases of AML with 11q23/*KMT2A* or AML

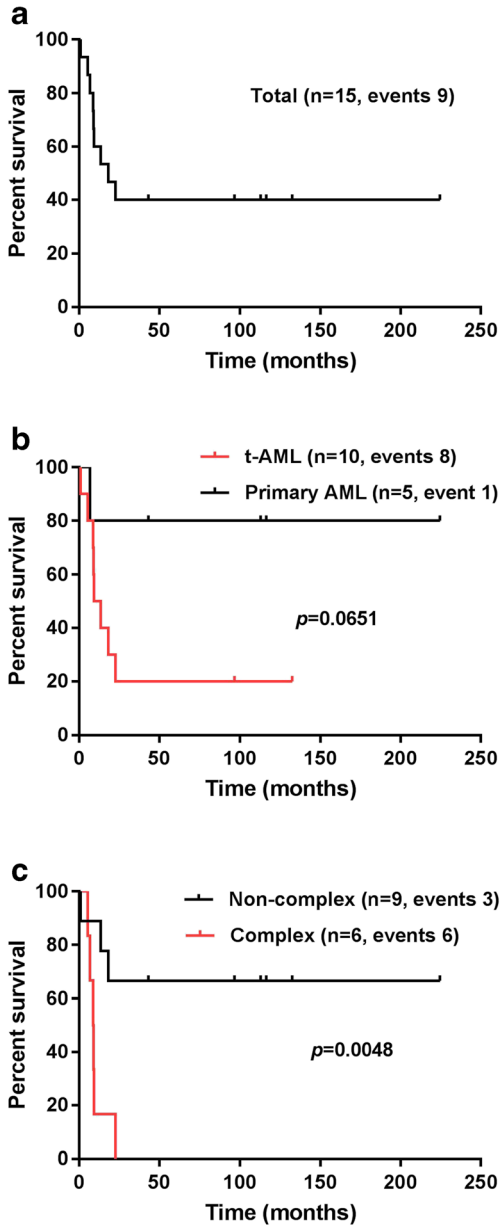

Fig. 3 Overall survival. **a** Overall survival of all 15 patients. **b** Comparison of the overall survival of patients with therapy-related AML vs. de novo AML. **c** Comparison of the overall survival of patients with non-complex vs. complex karyotype.

with t(8;16)/*KAT6A-CREBBP*, but is virtually absent in other AML subtypes and normal tissue [21]. *BRE* is required for the proper function of *BRCA1* (breast cancer 1)-mediated DNA damage repair [22] and overexpression of BRE in AML with 11q23/*KMT2A* has been associated with a favorable outcome [23, 24].

Two thirds of patients in this cohort had a history of malignancy (five breast cancer) and received cytotoxic therapies, including eight patients who received topoisomerase II inhibitors. The median interval from the initiation of cytotoxic therapy to the development of t-AML was 18 months, and all patients had AML without a preleukemic phase (MDS). These features are similar to other patients with t-AML that developed after topoisomerase II inhibitor therapies: short latency period, often present with overt AML without preceding MDS stage, and often associated with a balanced chromosomal translocation, with involvement of 11q23/*KMT2A* being the most common. In the previous studies of AML with t(8;16), about 34 to 76.7% patients had a history of malignancy and received cytotoxic therapies [1, 3, 4], breast cancer was the most common, 17 to 40% in different studies (supplemental Table 2) [1, 3, 4, 25]. The risk of developing t-AML or t-MDS is increased by exposure to chemotherapy, radiation, and growth-stimulating factors in breast cancer survivors [18]. In an earlier study, the authors suggested that the 3′ telomeric portion of the *KMT2A* gene has a scaffold attachment region which is vulnerable to translocation in the presence of topoisomerase II inhibitors [26]. Further studies are needed to clarify whether similar structures are also presented in *KAT6A* and/or *CREBBP* which make them more susceptible to topoisomerase II inhibitor exposure.

The bone marrow findings in patients with t(8;16)(p11.2;p13.3) are characterized by high blast count and monocytic morphology. The extramedullary involvement, DIC, and hemophagocytosis or erythrophagocytosis observed in this cohort are consistent with the findings in previous studies [1, 3, 5, 7–9]. In most cases, the blasts express granulocytic markers such as CD13, CD33, and MPO, as well as monocytic markers CD4, CD14, and CD64. About half of cases are positive for CD56. Notably, the parallel expression of MPO and NSE on blasts in most cases with t(8;16) set it apart from all other AML subtypes with monocytic differentiation [1, 27].

In previous reports, AML with t(8;16)/*KAT6A-CREBBP* in adults often had a short survival [1, 3, 4]. Patients in our cohort showed a superior survival (median OS, 18.2 months) compared with 4.7 months [1] or 8.5 months [4] reported in other studies. Notably, in our cohort, patients with de novo AML and/or patients with non-complex karyotype had an excellent OS (undefined median survival for both de novo AML and/or non-complex karyotype). Only when the patients had other adverse factors, like therapy-related AML (median OS, 11.4 months) or a complex karyotype (median OS, 8.9 months), the survival was poor. It has been reported that spontaneous remissions have occurred in neonates with AML t(8;16)(p11.2;p13.3) [9–12]. In a study by Coenen et al. [9], all seven neonates showed spontaneous remission of AML with t(8;16), and three remained in continuous remission. These observations suggest that a "watch and wait" policy might be applied in neonates AML with t(8;16). In contrast, spontaneous remission has not been observed in adults [1, 4, 9]. The CR rate after induction varies among different studies, ranging from 25 to 88.7%, [1, 4, 9] and the highest CR rate was reported in children (88.7%) [9] (supplemental Table 2). The CR rate in our cohort was 73%, higher than the previously reported adult case series [1, 4].

In summary, patients with AML with t(8;16)/*KAT6A-CREBBP* are often women who have a history of malignancy and exposure to topoisomerase II inhibitor therapy. These neoplasms often exhibit monocytic/monoblastic or myelomonocytic differentiation. In comparison with previously reported cases [1, 3, 4, 9], this cohort has a lower incidence of hemophagocytosis and DIC, and a better overall survival. Our data also suggest that de novo AML with t(8;16) and/or AML with t(8;16) and a non-complex karyotype are associated with excellent outcome.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a retrospective study and all procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

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